HC

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 22 1960

OHIO STATE UNIVERSITY NOV - 8 1960 LIBRARY

RECEIVED NOV 10 1960 HEALTH CENTER LIBRARY

TABLE OF CONTENTS

Faecal Incontinence in Children MARIAN COEKIN, M.B., D.C.H., and DOUGLAS GAIRDNER, M.A., M.D., F.R.C.P. 1175

Acute Respiratory Infections in Children
E. J. C. KENDALL, M.B., M.R.C.P.; G. T. COOK, M.D., and DORIS M. STONE, M.D., D.P.H. 1180

Is Universal Vaccination Against Pertussis Always Justified? JUSTUS STRÖM, M.D. 1184

Clinical Experience with Norethisterone and Norethisterone Acetate GEORGE L. FOSS, O.B.E., M.D. 1187

Treatment of Urinary Infections with Cycloserine
R. W. FAIRBROTHER, M.D., D.SC., F.R.C.P., and G. GARRETT, M.D., Dip.path. 1191

Neutralization of Heparin After Perfusion N. G. ROTHNIE, F.R.C.S., and J. B. KINMONTH, M.S., F.R.C.S. 1194

Transventricular Mitral Valvotomy During Pregnancy
J. M. REID, M.D., M.R.C.P.Ed., R. L. BERGER, M.D., and J. G. STEVENSON, M.D., F.R.F.P.S. 1197

Treatment of Severe Hypertension with Bretylium Tosylate E. F. D. MONTUSCHI, M.D., M.R.C.P., H. E. S. PEARSON, M.D., M.R.C.P., and L. L. WILSON, M.B., M.R.C.P.Ed. 1199

Drug Prophylaxis in Migraine RODNEY GRAHAME, M.B., M.R.C.P. 1203

PRELIMINARY COMMUNICATIONS

Ethionamide. R. W. RIDDELL, M.D., F.R.C.P.Ed., SHEILA M. STEWART, B.SC., PH.D., and A. R. SOMNER, M.D., M.R.C.P.Ed. 1207

MEDICAL MEMORANDA

Metastatic Carcinoma at the Site of Injection of Penicillin. T. S. WORTHY, PH.D., M.B., D.M.R.T., and E. J. C. WYNNE, M.Chir., M.B., F.R.C.S. 1208

BOOK REVIEWS 1209

CLINICOPATHOLOGICAL CONFERENCE

A Case of Pulmonary Hypertension 1219

GENERAL ARTICLES AND NEWS

B.M.A. Annual Clinical Meeting (continued) 1224
New Academic Year 1229
American Pathologists in Congress 1230
Medical Defence Societies 1231
The Jardin du Roi: Seedbed of Science 1231
To-day's Drugs 1233
OBITUARY 1241
MEDICO-LEGAL 1245
VITAL STATISTICS 1246
MEDICAL NEWS 1248
QUESTIONS AND COMMENTS 1251

LEADING ARTICLES

Health Services in the Federation of Rhodesia and Nyasaland 1213
Buerger's Disease 1214

ANNOTATIONS

Immunization Against Whooping-cough 1215
Salicylate Poisoning 1216
Nerve Endings in Myasthenia Gravis ..1217
Institutions for the Subnormal 1217
Prescribing Simplified 1218

CORRESPONDENCE

Statistics of Road Accidents. N. I. SPRIGGS, F.R.C.S. 1233
Child Psychiatry. LOUISE F. W. EICKHOFF, D.P.M. 1234
Faulty Anaesthetic Apparatus. J. MCNAUGHT INGLIS, F.F.A. R.C.S. 1234

SUPPLEMENT

Full Contents on First Page of Supplement

Private Practice Committee 169
Organization Committee 170
Public Health Committee 171
Correspondence:
Poor Service in Casualty. S. H. F. HOWARD, M.B. 173
Compensation and Superannuation. C. H. BARBER, D.M. 173

CORRESPONDENCE—*contd.*

Gangrene from Thiopentone. J. H. BURN, M.D., F.R.S. 1235
Megimated Barbiturates. R. NEVILLE, D.P.M. 1235
Phenothiazine Derivatives. T. J. C. WARRINER, M.D. 1235
Congenital Talipes. D. E. MARGARET PIERCE, D.C.H. 1236
Bastard Dosage. A. P. M. PAGE, M.D. 1236
Estimation of Faecal Fat. R. VAUGHAN JONES, M.R.C.P. 1236
Adiposity. JOHN H. SWAN, M.R.C.S. ..1237
Mental Health. W. A. HEATON-WARD, D.P.M. 1237
School Phobia. R. T. D. FRANKLIN, M.B., D.P.M. 1238
Eradication of Malaria. C. GÖKBERK, M.D.; R. B. HEISCH, M.D. 1238
Origins of Life. A. E. SLATER, M.R.C.S. 1238
Fate of the Claudicator. A. SINGER, F.R.C.S. 1239
Our Hospitals. E. J. R. BURROUGH, M.A. 1239
Subluxation of Sternoclavicular Joint. R. G. WILLIAMS, M.B. 1239
Marksmanship and Crossed Laterality. B. S. PHILLIPS, D.P.M. 1239
Lumps in the Breast. MALCOLM DONALDSON, F.R.C.S. 1239
Personal Record Cards. JOHN RIDDELL, M.D. 1239

Letters on other subjects on pp. 1240–1

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1

No. 5207, WEEKLY, PRICE 3/-

Copyright © 1960

REGISTERED AS A NEWSPAPER

BROXIL - THE HIGH PEAK PENICILLIN FOR BETTER CLINICAL RESULTS

REGD. TRADE MARK

'In short, with the possible exception of bacterial endocarditis, "broxil" should be given when previously Penicillin G or V has been used.' *Practitioner* (1960), **184**, 793.

Broxil, the penicillin of choice, is now available in tablet and syrup forms for convenient oral administration. **BROXIL TABLETS** available in strengths of 125 and 250 mg. **BROXIL SYRUP**—bottles of 60 ml. when dispensed (each 5 ml. contains 125 mg).
Broxil is the potassium salt of 6-(alpha-phenoxypropionamido) penicillanic acid.

BEECHAM RESEARCH Laboratories LTD · BRENTFORD · ENGLAND

BRL

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 22 1960

FAECAL INCONTINENCE IN CHILDREN

THE PHYSICAL FACTOR

BY

MARIAN COEKIN, M.B., D.C.H.
Research Assistant in Paediatrics

AND

DOUGLAS GAIRDNER, D.M., F.R.C.P.
Paediatrician, Addenbrooke's Hospital, Cambridge

The question of the different causes of faecal incontinence in children has evoked surprisingly little attention. Until 1948 there was inevitably confusion about the relationship between the various forms of colonic dysfunction (with or without megacolon) which are encountered in children, but in that year the work of Swenson and Bill led to the defining of Hirschsprung's disease as obstruction due to an aganglionic segment of bowel. This left the way open for the study of non-obstructive forms of megacolon in children. Bodian, Stephens, and Ward (1949), in describing a series of 34 of these cases under the term "idiopathic megacolon," thus referred to the faecal incontinence which is often an accompaniment of the constipation: "Some children in this group displayed features which might be interpreted as psychogenic. As a result of pain on defaecation they develop a 'fear of the pot.' They seem to prefer to defaecate in the standing position, and they stiffen knees and hips and lie back in the supine position if forced to use the pot; presumably this position affords them the least discomfort in the act of defaecation. The fear of the pot, the soiling of the hands and clothes due to overflow incontinence, and the natural shame about these unpleasant features are rapidly and completely eliminated by physical treatment of the constipation and therefore do not appear to be psychogenic."

This mechanistic view of soiling as resulting from inadequately treated constipation has by no means gained universal acceptance; on the contrary, almost everything that has been written in the last decade has viewed the subject from the psychological standpoint, and an emotional basis for soiling has been tacitly assumed. In keeping with this assumption, in the United States cases of incontinence associated with constipation are commonly referred to under the heading of "psychogenic obstipation," for which the treatment is, to quote the laconic advice of a standard paediatric text, "psychiatric for both parents and child" (Nelson, 1959).

It is against a background of these two opposing viewpoints that we have, since 1949, studied all children presenting with faecal incontinence, with the intention of arriving at some conclusion regarding aetiology in each case. We here present an analysis of 69 cases of soiling treated during the 11-year period 1949–59. We have excluded children with severe mental retardation, those with an ectopic or stenosed anus, and those with spinal disease such as meningomyelocele.

It early became clear that most of the soilers tended to fall naturally into one or other of two main groups. In one group (44 cases) the soiling could be most simply accounted for on a mechanical basis, with constipation as the *primary* condition, any emotional disturbance which might be present being a consequence of the soiling and constipation. In the other group (15 cases) the primary disturbance was judged to be psychological, with constipation, if present, a secondary phenomenon. There remained a smaller number (10 cases) in whom mechanical and psychological factors were so inextricably interwoven that we could not point to either one as primarily concerned.

This differentiation of the majority of soilers into two broad groups was made initially on the history, but received some support from the often differing physical findings in the two groups, and in due course proved justified when the response to the appropriate treatment came to be assessed. Some of the differences between the clinical features of the two groups are set out in the Table.

Clinical Features of Two Types of Faecal Incontinence

	Mechanical (Colonic Inertia) (44 Cases)	Psychogenic (Encopresis) (15 Cases)
Sex incidence	Equal (M 21, F 23)	Male preponderance (M 10, F 5)
Age of onset of soiling	Usually below 4 years (34 cases, 77%)	At any age
History of constipation in first 6 months of life	Often (12 cases, 27%)	Seldom (1 case)
Abdominal faecal masses palpable	Often (26 cases, 59%)	Less often (2 cases)
Rectum loaded with faeces	Usually (36 cases, 82%)	Less often (7 cases)
Evidence of emotional disturbance	Often inconspicuous	Conspicuous
Response to physical treatment of constipation	Generally good	Poor
Response to psychotherapy	None	Fair

Incontinence the Result of Mechanical Factors (Colonic Inertia)

In this group constipation was judged to be the initial event and an overflow incontinence one of its consequences, with psychological factors playing at most a secondary part. A typical sequence of events is as follows.

The child often differs from his sibs in having given trouble with constipation from the first few weeks or months of life, passing infrequent hard blood-streaked stools with obvious straining. Such a history of constipation in the first six months of life was present in 12 of 44 cases (27%). In the second year these symptoms tend to become more prominent, with occasions when the bowels open at intervals of a week or longer and with the passage of huge stools of often astonishing calibre. Their passage is achieved only after hours of tears and travail, and indeed the hard faecal mass eventually passed may be, in proportion to the size of the patient, comparable to that of the foetal head.

Cases seen at this stage will respond gratifyingly to the energetic treatment of the constipation, and in that event soiling does not develop. Unhappily, it is often not recognized that the child requires such treatment, and he increasingly retains his faeces as long as he can, in order to postpone the now inevitable pain of defaecation. A state of retention with overflow follows, with liquid faeces oozing past the incarcerated faecal masses, which distend the rectum and lower colon. When he does finally come to defaecate, he commonly finds it less intolerable to do so either standing, or lying on his back with legs stiffly extended and adducted, so that at this stage "pot-refusal" has a purely mechanical explanation.

There are many variations on this general theme. In some children the accumulation of faeces is more insidious, with painful defaecation and pot-refusal less prominent features. In others constipation is at first slight and gives little trouble until some upset in the child's rhythm occurs, such as an acute illness, a change of residence, or the illness of the mother. In a number of our cases the start of bowel disturbance dated clearly from a period when defaecation had made the child scream with pain, strongly suggesting that he had originally had an anal fissure (Apley, 1954). Once faecal accumulation has begun, from whatever cause, it is easy for a vicious circle to be set up—pain or difficulty in passing an outsize stool leading to further faecal retention, which in turn causes overdistension of the bowel and a gradual loss of the normal evacuation reflex, leading to the usual overflow pattern of soiling. In a surprising number of our cases such overflow incontinence had been mistaken for diarrhoea.

Examination of the abdomen generally shows little if any distension, but faecal masses are often palpable. The examining finger can be easily and painlessly inserted into an anus which is rather lax than otherwise, to enter a rectum filled with faecal material, which may consist either of rocky-hard masses, or of semi-liquid faeces which have leaked past the inspissated masses higher up. In spite of a past history often suggesting that an anal fissure has earlier been present, in none of our cases was a fissure found by the time the child was examined.

Psychological Factors

Although some children assigned to this "mechanical" group of soilers showed behaviour disorders, in general these were more conspicuous by their slightness, considering the painful and shaming nature of the child's bowel symptoms, their long standing, and the fact that all too often these symptoms had been misinterpreted. Such misinterpretation had caused some children to be treated by punishment for "naughtiness," some by opium and chalk for "diarrhoea," and others by prolonged psychiatry. How much difficult behaviour, might it be asked, may a young child legitimately be allowed, if his soiling due to severe constipation is treated for months by anti-diarrhoeal measures, or his reasonable fear of painful defaecation be attributed to an emotional conflict and aperients therefore deliberately withheld? In such circumstances we have repeatedly been struck by the child's stoic acceptance of such insults, and humbled by his readiness to forgive and forget so soon as his miseries have been properly relieved.

Radiological Findings

In the early part of this study barium-enema examinations were freely carried out. The findings differed from case to case mainly in degree, and were of two kinds. (1) In all of 19 cases there was undue distensibility of the rectum and sigmoid and occasionally of most of the colon also, so that in extreme cases 1 to 2 litres of the contrast medium could be run in without causing the child any discomfort or any urge to defaecate. (2) In 13 out of 19 cases there was poor evacuation, the colon, when it did respond to distension, contracting weakly and emptying incompletely.

These findings, which are in keeping with those of Bodian *et al.* (1949) and Bodian (1952), are best described as *colonic inertia** rather than as "idiopathic megacolon," since after treatment of the constipation the colon tends gradually to regain more normal tone and its size and distensibility diminish.

In more recent years we have rarely subjected these cases to radiological examination, for it adds little to what can be learned clinically, besides exposing the child's gonads to radiation. Differentiation from the much rarer Hirschsprung's disease (six cases seen in the same 11-year period) can usually be made clinically, since obstructive signs, which are typical of Hirschsprung's disease, are noticeably uncommon in colonic inertia. Exceptionally, however, cases of colonic inertia have presented in the *neonatal* period with an obstructive picture (see Cases 2, 3, and 4), closely mimicking Hirschsprung's disease. Differentiation of the two conditions by radiological means may then be required (see Figs. 1, 2, and 3).

Treatment

Initially one or more enemas are usually required to empty the lower bowel. This can generally be done either in the out-patient department of the hospital or by the district nurse at home, and only a few children have required hospital admission. Once the bowel has been emptied it must be kept so by the use of aperients of the colon-stimulating group such as phenolphthalein or senna, given in regular and adequate amounts. We have come to rely on only two preparations: (1) Phenolphthalein 1.3% in 50% liquid paraffin emulsion, up to 6 teaspoonfuls daily; and (2) standardized senna ("senokot"), up to 4 tablets daily.

In the earlier stages of treatment, when the child's confidence in his ability to pass a stool without pain must be restored, the lubricant action of the paraffin preparation is particularly valuable. The mother is told to adjust the dose of these two preparations, usually giving both at first and in divided doses, so that the child passes a softish stool about once a day, a proper consistency being the main guide to dosage. Large doses may be needed at this stage. After normal rhythm has been achieved it is often adequate to continue with only

*The term "colonic inertia" was first applied to these cases by Mr. Denis Browne.

one aperient, and, as paraffin given prolongedly may possibly be carcinogenic, senna is preferable†

The dosage of aperient is tapered off as symptoms allow, but it is impossible to predict how long treatment will need to be maintained, as this may vary from a few weeks to a term of years. We have not found dietetic measures effective in modifying the severe states of constipation here considered.

Results of Treatment

Two types of response were apparent in the mechanical group of soilers. In one group soiling was on a simple overflow basis; when these children's constipation was adequately treated their soiling usually ceased at once. The other group was composed mainly of those children in whom painful defaecation had played a major part in the past and who had discovered that they could gain relief by adopting some peculiar position for defaecation, usually standing up. This habit of defaecating standing might be prolonged for a long time after medical treatment had effectively removed all cause for pain. Several months might then be required for the child to rediscover the technique of normal defaecation and to accept the fact that he was able to sit on the pot to defaecate without risking severe pain.

In 38 of the 44 cases (86%) treatment was judged to be satisfactory: 19 of these permanently ceased to soil once the initial emptying of the bowel had been achieved and the correct dosage of aperient established; a further 10 attained a similar permanent cure but took from 2 to 12 months before bowel control was secure; and nine more quickly acquired good control, except for isolated lapses due often to a failure to maintain the prescribed regimen.

In the remaining six cases (14%) the response was less satisfactory. Results inevitably depended in large measure on the skill of the mother in adjusting the day-to-day dose of aperient, and, with one exception, all the failures could be accounted for by the incapacity of the mother in this respect. The exception was a boy who seemed incapable of achieving secure bowel control, until at about the age of 6 years he for the first time developed the sensation of an urge to defaecate (see also Case 2 in this context).

Incontinence the Result of Psychogenic Factors (Encopresis)

In this group psychogenic factors were judged to play a primary or predominant part. Of the 15 cases 10 were boys; a similar male preponderance has been noted in other series of psychogenic soiling—for example, 6:1 (Anthony, 1957), 5:1 (McTaggart and Scott, 1959), and 2:1 (Pinkerton, 1958). This contrasts with the approximately 1:1 sex ratio amongst our 44 cases of soiling from mechanical causes.

In these children constipation played a variable part. A history of constipation in the first six months of life was present in only 1 out of 15 cases. Faecal masses were found in the abdomen in only 13% and in the rectum in 47%. These figures should be compared with the findings in the mechanical group of soilers (see Table). Retention of faeces, when present, was judged to have been a subconsciously purposive act, initially at least.

In the majority of this group, however, constipation was chiefly conspicuous by its absence, and the stool passed was of normal consistency, but was studiously deposited by the child in the wrong place.

Thus most of these children were from the first interview clearly to be differentiated from the previous group by the fact that constipation was demonstrably not present, nor was the incontinence of the retention-with-overflow pattern. Nearly all these children also showed obvious signs of emotional disorder apart from their bowel symptoms, and many came from unsatisfactory homes. A few children had never received any training from a mother who was either hopelessly overburdened or mentally retarded (Anthony, 1957).

This group of cases is discussed only briefly here, partly because we have tended to refer these children to colleagues in child psychiatry, and partly because of the extensive attention this group of soilers has already received in recent psychiatric literature (Anthony, 1957; Pinkerton, 1958; McTaggart and Scott, 1959). We suggest that the term "encopresis" should be confined to psychogenic incontinence. The word was coined by Weissenberg (1926) as an analogue to enuresis, to imply faecal incontinence without organic cause; it should therefore not be applied to cases of incontinence due to colonic inertia, if the latter is to be regarded as a congenital or constitutional disorder. Evidence in favour of such a view is presented later.

Treatment

Treatment is necessarily along psychiatric lines, but the important question arises how far physical methods should be used in conjunction. Pinkerton (1958), in his entertaining paper on "psychogenic megacolon" in children, argues in favour of deliberately withholding aperients in order to underline and fortify the psychiatrist's explanation to the parents that the child's symptoms are emotional in origin. Certainly there are cases where the child's retention of faeces is subconsciously a highly purposive act; in such circumstances to force a child to part with his faeces by ordering an enema might well be the worst approach. Yet equally is it wrong to take up so doctrinaire a stand on this matter as to withhold the normal treatment from a child with severe faecal impaction, merely because impaction is the end-result of an emotional disorder. Such an approach is surely a *reductio ad absurdum* of the policy of "symptom tolerance," which Winnicott (1953) has urged paediatricians to adopt towards the somatic symptoms of emotionally disturbed children.

Clearly, each case needs to be considered individually and, where appropriate, physical and psychiatric treatments used in conjunction. The following case is illustrative.

Case 1.—This boy first became constipated at the time he started school at 5 years. A few months later soiling was added to the picture, and his doctor then found that he had faecal impaction with overflow incontinence. This was treated with an enema, with a cessation of soiling for two weeks, but subsequently soiling recurred. On examination, when aged 6 years, there was no abdominal faecal mass but the rectum was filled with soft faeces. A number of other symptoms of emotional origin were present, such as temper tantrums and insomnia, and his soiling was judged to have an emotional origin. He was referred to a psychiatrist, who treated him for the next 12 months, without, however, any

†Robert Burton in his *Anatomy of Melancholy* (1621) thus extols the virtues of senna: "A wonderful herb against melancholy, it scours the blood, lightens the spirits, shakes off sorrow, a most profitable medicine." Burton's words perhaps have some relevance to our present thesis, that the emotional symptoms of a child with constipation may at times be more logically dealt with by an aperient than by psychiatry.

improvement in his soiling, which occurred regularly several times each day. He was therefore reviewed at this stage, the main physical finding being again that the rectum was filled with soft faeces. In conjunction with the psychiatrist, it was concluded that it would now be worth while to try to treat his bowel symptoms by physical means. He was given an enema to empty his lower bowel, and thereafter regular doses of an aperient. Soiling ceased forthwith and he remained clean subsequently. His psychological state also improved from this time, although he still retained a number of problems which required continued psychotherapy.

Validity of Dividing the Causes of Soiling into Somatic and Psychic

To make a separation of this kind is unfashionable, but we have been led to do so on the grounds of a commonsense appraisal of these children's problems. Firstly, there is no evidence in many soiling children of an adequate emotional cause for their symptoms. Secondly, those children whose soiling has been ascribed to mechanical causes have in most instances duly responded to simple treatment of constipation.

We have already referred to the common assumption that all soiling children are suffering primarily from an emotional disorder. Thus Pinkerton (1958), writing on the syndrome of chronic constipation with megacolon and overflow incontinence, holds that "while colonic inertia forms the immediate basis of the disorder, its ultimate aetiology is psychogenic in nature," though he bases this conclusion on selected case material, the children in his series being "referred for psychiatric opinion either because of their unsatisfactory response to standard treatment measures or because the disorder was suspected to have an emotional basis." That other psychiatrists similarly tend to see a selected group of soiling children, with a high incidence of psychogenic cases, became clear when, at a meeting of the Society for Psychosomatic Research (in London, May, 1959), the subject was discussed by a group of paediatricians and child psychiatrists.

The facts are: (*a*) that a child with overflow incontinence due initially to mechanical factors may acquire superimposed emotional symptoms; and (*b*) that retention of faeces may be initially psychogenic yet lead to a state of overflow incontinence identical with that caused by mechanical factors. While, therefore, it is true that many cases of soiling are due to the interplay of multiple factors, this does not exonerate the physician from the duty of attempting to elucidate the *main* factors in each case. This we found possible in 59 of our 69 cases, leaving only 10 where somatic and psychic factors were so interwoven that separation of the two seemed impossible.

Constipation as a Congenital Disorder

In describing the cases of soiling from colonic inertia we noted that in 27% there was a history of constipation in the first six months of life. Alongside the present study of children with soiling we have observed an approximately equal-sized group of children with severe constipation without soiling. In these, too, the constipation often dates from the early months or weeks of life. The following three cases illustrate constipation severe enough in the neonatal period to cause an obstructive picture, which later changed to a typical picture of colonic inertia.

Case 2.—A full-term male baby passed four stools, all meconium, over the first five days. On day 5 a picture of lower-bowel obstruction developed, with bilious vomiting and distension. A radiograph showed dilated loops of bowel with fluid levels (Fig. 1). A barium enema showed a large distensible sigmoid, which evacuated poorly (Fig. 2). After this examination a large amount of meconium and flatus was passed and the distension was relieved, but 48 hours later a further radiograph showed much barium still retained in the sigmoid (Fig. 3). During the next three weeks the bowels moved satisfactorily, but at 4 weeks of age they ceased to do so, some distension recurred, and he was started on regular doses of aperient. Severe constipation persisted for the next eight years; during this period

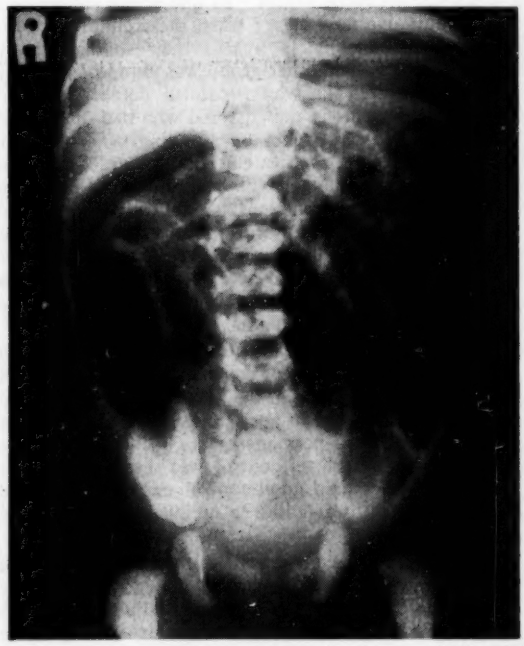


FIG. 1.—Case 2, aged 5 days. Obstructive picture with distended loops of bowel and fluid levels (not discernible in reproduction).

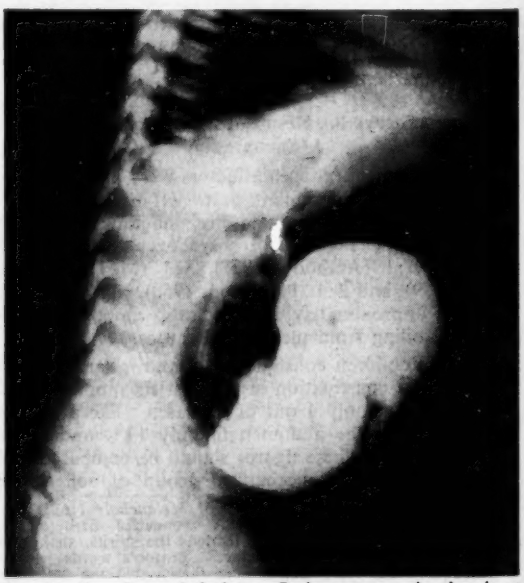


FIG. 2.—Case 2, aged 5 days. Barium enema showing large distensible inert sigmoid. No constant narrowed segment.

he remained well so long as regular large doses of aperients were given, supplemented until the age of 4 by repeated enemas, but if any attempt was made to omit this treatment faecal retention recurred, with faecal masses filling the abdomen. His mother was skilful in detecting this and arranging for an enema to empty the bowel, so that at no time was soiling added to the picture of constipation. At the age of 8 he acquired for the first time the sensation of the desire to defaecate, and thereafter was able steadily to reduce the amount of aperient needed. He is now 9½ years and has a normal bowel function while taking minimal doses of aperient. A series of barium-enema examinations were made, the first at 5 days and the last at 5¼ years. Distension of the sigmoid was present on every occasion, the rest of the large bowel being less affected. Up to 3 years of age evacuation was exceedingly poor, but thereafter there was a gradual improvement in this respect, except that invariably the sigmoid failed to empty (Fig. 4). (No narrowed segment of bowel was present.)

FIG. 3.—Case 2, aged 7 days. Distension relieved, but 48 hours after barium enema much barium still retained in large bowel.

FIG. 4.—Case 2, aged 5¼ years. Barium enema, post-evacuation. Sigmoid and rectum still showing very poor evacuation.

Case 3.—A premature female baby weighing 3 lb. 6 oz. (1,530 g.) passed no stool between the third and sixth days, when she developed severe distension. This was temporarily relieved after an enema which gave a large faecal result, but recurred over the next 10 days. A number of enemas were given with decreasing effect, but injections of neostigmine 0.1 mg. effectively caused evacuation of faeces and flatus. At 3 weeks she started to thrive and was discharged from hospital at 6 weeks. Thereafter, though breast-feeding well, she gradually became increasingly constipated, passing infrequent hard motions with difficulty. On large doses of aperient, supplemented by frequent enemas and suppositories, fairly normal bowel function was achieved. After 6 years she was able to decrease the amount of aperient and at 6½ years to omit it altogether. A barium-enema examination at 1 year was normal, but at subsequent examinations at 2 and 4 years the colon was large and unduly distensible, and evacuation was delayed and inefficient. At 5 years the colon was still large and distensible but evacuated much better.

Case 4.—A full-term male baby passed meconium just after birth but not subsequently. On day 2 bilious vomiting set in, and on day 3 a radiograph showed distended loops of gut with fluid levels. A catheter inserted in the rectum initiated the passage of a large amount of meconium, but during the subsequent week stools were passed only after enemas. He was discharged from hospital at 10 days and was next seen at 8 months, with a history that he had never had his bowels open unless given some local stimulus, supplied digitally by the mother at about weekly intervals, when he would pass an abnormally large stool. Examination revealed hard faeces filling the rectum. He was put on large daily doses of aperient and as long as he continued on this regime he maintained normal bowel function.

It is significant that in none of these three cases of congenital constipation did soiling develop, since all came under medical care at an early stage and were given adequate treatment for the constipation. The following case is a more typical example of congenital constipation inadequately treated and going on to develop soiling; this girl is of interest as being one of twins.

Case 5.—One of non-identical twin girls, each of whom weighed about 6 lb. (2,720 g.) at birth, at 6 weeks began to pass infrequent hard blood-streaked stools with much straining. Various aperients in small doses were tried without much effect, and by 9 months her symptoms were worse, with soiling added to the picture; the bowels would remain unopened for up to nine days, at the end of which time a suppository would cause the painful evacuation of an enormous stool. She remained physically well, but became increasingly irritable and "difficult." When first seen at 2 years faecal masses were palpable in abdomen and rectum. These were evacuated with an enema and thereafter she was maintained on aperients given in much larger doses than formerly. She had regular bowel actions on this regime, and soiling ceased forthwith, her mother reporting that her behaviour difficulties vanished along with the restoration of normal bowel rhythm. One year later, aged 3, she was beginning to need smaller doses of aperient. Her twin sister was in striking contrast, as she maintained normal bowel function at all times without any aperient.

Cases such as the four quoted leave no doubt of the existence of constipation as a congenital disorder. We are then left with the fact that in only 27% of our group of cases of soiling from colonic inertia was there a history of constipation in early infancy. We can but speculate on whether in the remaining 73% of our cases of colonic inertia a congenital factor, though unexpressed in the early months, may have provided a basis for the later development of bowel symptoms, triggered off, as these so often appear to have been, by quite trivial incidents.

Summary and Conclusions

During an 11-year period 69 cases of faecal incontinence in children were studied.

In 44 cases (64%) soiling was judged to be mechanical—that is, the consequence of constipation. Soiling of this type had often been misinterpreted, but when the constipation was treated the soiling usually ceased.

Evidence is presented for the existence of constipation as a congenital disorder: this, if untreated, may later lead to an overflow incontinence.

In 15 cases (22%) the incontinence was judged to be psychogenic; these children required psychiatric treatment. Constipation was present in only a minority of this group, but might then require physical treatment in conjunction with psychiatric.

In only 10 cases (14%) were somatic and psychic factors so interwoven that neither could be ascribed a primary role.

We are indebted to Dr. F. R. Berridge and to the late Dr. B. Donnelly for the radiological work; to Dr. B. F. Whitehead for much psychiatric assistance; to past

paediatric registrars, especially Drs. S. Mason and N. Rothfield, who shared our interest in this subject; and to Dr. Janet Roscoe, whose collaboration and criticism have been of equal value. One of us (M.C.) is in receipt of a grant from the Beebe Fund.

REFERENCES

Anthony, E. J. (1957). *Brit. J. med. Psychol.*, **30**, 146.
Apley, J. (1954). *Practitioner*, **172**, 171.
Bodian, M. (1952). Ibid., **169**, 517.
—— Stephens, F. D., and Ward, B. C. H. (1949). *Lancet*, **1**, 6.
McTaggart, A., and Scott, M. (1959). *J. Pediat.*, **54**, 762.
Nelson, W. E. (1959). *Textbook of Pediatrics*, 7th ed., p. 655. Saunders, Philadelphia.
Pinkerton, P. (1958). *Arch. Dis. Childh.*, **33**, 371.
Swenson, O., and Bill, A. H. (1948). *Surgery*, **24**, 212.
Weissenberg, S. (1926). *Z. Kinderheilk.*, **40**, 674.
Winnicott, D. W. (1953). *Proc. roy. Soc. Med.*, **46**, 675.

ACUTE RESPIRATORY INFECTIONS IN CHILDREN

ISOLATION OF COXSACKIE B VIRUS AND ADENOVIRUS DURING A SURVEY IN A GENERAL PRACTICE

BY

E. J. C. KENDALL, M.B., M.R.C.P.
General Practitioner

G. T. COOK, M.D.
Public Health Laboratory, Guildford

AND

DORIS M. STONE, M.D., D.P.H.
Public Health Laboratory, Epsom

Respiratory infections are among the commonest illnesses encountered in general practice. Records have shown that their incidence is highest in childhood (Lidwell and Sommerville, 1951; Logan and Cushion, 1958). Only a portion of these illnesses have been found to be due to bacteria, and it has long been assumed that the remainder are due to virus infections. With the introduction of tissue-culture methods for viral propagation, it has become possible to test comparatively simply for the presence of certain viruses. HeLa cell cultures, though of only limited value in the isolation of upper respiratory viruses, are easily maintained in the laboratory and were employed in this investigation. This paper reports the results of virological and bacteriological examination of throat swabs from cases of febrile respiratory illness occurring among children in a general practice. Clinical observations were also made. Stool cultures, which might have increased the number of virus isolations, were not carried out. It was hoped that these studies would reveal the aetiology of a proportion of the acute respiratory infections occurring in this group of children.

Materials and Methods

The population studied were all registered on the National Health Service list of one of us (E. J. C. K.). This general practice is situated in a Surrey town on the south-west fringe of London. All social groups were represented, with a preponderance of clerical and skilled manual workers. Children up to the age of 18 were included in the survey; the age constitution of this group as it was on June 30, 1958, is set out in Table I. During the period of the survey 129 children joined the group and 117 left it.

TABLE I.—*Respiratory Infections from June 1, 1957, to December 31, 1958. Age Distribution of Patients Investigated and Principal Virological and Bacteriological Findings*

Birth Years	No. in Group	All Respiratory Infections	No. Investigated	Coxsackie B Virus	Adenovirus	*Str. pyogenes*
1939–43	125	76	8	1	—	2
1944–48	170	162	21	4	—	2
1949–53	190	290	86	11	3	11
1954–58	110	174	31	4	1	3
Total	595	702	146	20	4	18

The survey extended over the period June 1, 1957, to December 31, 1958. Observations were not made, however, from August 26 to September 25, 1957, from April 17 to May 1, 1958, and from August 25 to September 23, 1958.

Illnesses included in the study comprised those occurring in children who saw their doctor during the first five days of a febrile respiratory infection. Those who developed specific fevers or who were considered on clinical grounds to be suffering from influenza were not included. Symptoms were listed according to an agreed schedule, and the physical findings were recorded in a standard manner. As often as possible, twice-daily temperature readings were made by the parent. A follow-up visit was made one to three days later, or at the end of the illness.

Laboratory Methods.—Two swabs, mounted on wooden applicators, were fixed in parallel in one cork and sterilized together. This composite swab was applied to the tonsillar fossa. One swab was then used for bacteriological examination (D.M.S.) and the other was broken off into 2 ml. of Hanks's solution containing penicillin (100 units/ml.), streptomycin (100 μg./ml.), and neomycin (50 μg./ml.). This mixture was frozen in solid CO_2 snow in a vacuum flask and later held at −20° C. until a virological examination was made (G.T.C.).

Virus Examination.—Virus isolations were attempted in HeLa cells grown in Hanks's solution with antibiotics (as above), containing, in addition, 0.2% lactalbumin hydrolysate (final concentration), 10% horse serum, and 10% rabbit serum. For maintenance, 3% rabbit serum was used.

Amounts of 0.2 ml. of fluid were added to each of two tubes of HeLa cells. Cultures were incubated at 37°C. and examined every second or third day for 8 to 10 days. At the end of this period blind passages were always carried out, the cultures of the first passage being examined for a further 8 to 10 days before being discarded.

When cell changes occurred neutralization tests were carried out with poliomyelitis and Coxsackie B antisera. Adenovirus was identified by means of a complement-fixation test.

Bacteriological Examination.—Immediately on receipt, throat swabs were plated on layered-blood-agar and laked-blood-tellurite plates. Films were made, stained by Gram's method, and examined microscopically. Plates were incubated aerobically overnight and the flora identified by the usual criteria. Colonies of haemolytic streptococci were picked off and tested by Maxted's (1953) bacitracin sensitivity method. Any which proved not to belong to group A were subcultured and their group was identified by Lancefield's technique. For the purposes of this investigation, streptococci other than those belonging to group A were ignored.

Pneumococci were further investigated only when they were without doubt the predominant organism on the blood-agar plates. They were subcultured in dextrose broth, if necessary repeatedly, and the smooth suspensions thus obtained were tested by slide agglutination against the only sera available to us, types 1–3. The investigation was carried out to determine whether, where no other infective agent could be isolated from patients, there was a constant type of pneumococcus present, suggesting that this had an aetiological significance.

Results

Of 702 acute respiratory illnesses reported among members of the group during the period of study, 146 came within our terms of reference and were investigated. The results are summarized in Table I. Coxsackie B3 virus was isolated on 19 occasions (once in association with an adenovirus) and Coxsackie B4 virus from one case; 13.7% of all cases investigated were thus associated with these viruses. Adenoviruses types 1, 2, 3, and 4 were isolated from four cases (2.7%). *Streptococcus pyogenes* was found in 18 (12.3%) of the cases. Poliovirus was not isolated. Thus in 41 (28.1%) of the cases one or more potential pathogens were discovered in association with acute illness. The clinical findings for each group are compared in Table II.

TABLE II.—*Principal Symptoms and Signs in Three Groups of Acute Respiratory Illness*

	Coxsackie B Virus (19 Cases) %	*Str. pyogenes* (18 Cases) %	Undifferentiated Respiratory Infections (25 Cases) %
Headache	84	78	60
General muscle aches	47	33	32
Nasal symptoms	53	83	84
Sore throat	58	83	72
Cough	42	72	68
Gastro-intestinal symptoms (nausea, vomiting, diarrhoea)	63	50	56
Moderate or severe throat changes	47	94	44
Follicular exudate in throat	11	39	12
Moderate or severe lymph-node enlargement	42	67	28
Tender cervical lymph nodes	21	56	16
Average maximum temperature*	102·1° F. (37·9° C.)	102° F. (38·9° C.)	101·7° F. (38·8° C.)
,, duration of fever*	3·2 days	2·9 days	3·2 days

* Refer to 11, 13, and 21 cases respectively.

Coxsackie B Virus Infections

A variety of illnesses were associated with this virus. In nine cases a short febrile illness began with sore throat and general symptoms of malaise, headache, and shivering. The pharyngeal changes in these cases were moderate or severe. In a further six cases the constitutional symptoms predominated, the throat being either unaffected or only slightly sore, with, at most, slight changes in the upper respiratory tract. Moderately severe myalgia (thoracic or abdominal) occurred in two cases, bronchiolitis in one, and in one further case a moderately severe but transient meningeal reaction dominated the illness. The case in which a double infection occurred with adenovirus and Coxsackie B3 virus is described later under adenovirus infections.

Fever reached to between 100 and 103° F. (37.8 and 39.4° C.) in the majority and lasted two to four days. When affected the pharynx was reddened and oedematous, but showed exudate in only two cases. Vesicles were absent, but in two cases greyish plaques 1–2 mm. in diameter without erythema were seen on the soft palate towards the end of the illness. Cervical lymphatic-gland enlargement was never prominent and only slight conjunctival reddening was seen. Bronchiolitis, encountered once, was the sole manifestation of involvement of the lower respiratory tract. In general the physical signs were scanty in relation to the severity of the illness. No complications or relapses occurred, but convalescence was slow for so short a fever.

The following three cases illustrate the range of infection.

Case 1.—A boy, aged 10, awoke in the night of August 12, 1958, with a severe headache, and vomited twice. The next morning he had a frontal headache, was lethargic, disliked the light, and complained of a stiff neck. On examination he was moderately ill with a temperature of 103° F. (39.4° C.). He had slight redness of the throat and palpebral conjunctivae, gingivitis, and a moderate neck-stiffness, with pain in the mid-thoracic region on flexion of the cervical spine. There were no abnormal signs in the chest, and the lymphatic glands were not enlarged. In the evening his headache was severe but he had not vomited further. He was flushed and had a puffy face, but his neck was less stiff. His temperature was 102° F. (38.9° C.). The next day (third day of illness) he was feeling and looking much better and his temperature had become normal. He had only slight pain in the mid-thoracic spine on flexion of the neck. By August 20 he felt fit and energetic and there were no abnormalities on examination. Coxsackie B3 virus was isolated from a throat swab taken on August 13. Serum taken on August 14 neutralized Coxsackie B3 virus to a titre of 1/160, and by August 20 the titre had risen to 1/640. *Family History*:—His mother and father were not affected. One brother had an acute febrile pharyngitis and herpetic stomatitis, but Coxsackie virus was not isolated from his throat swab. Herpes simplex virus was isolated, however. Another brother remained well. Two months later sera from these two boys neutralized Coxsackie B3 virus to a titre of 1/640 and 1/1250 respectively.

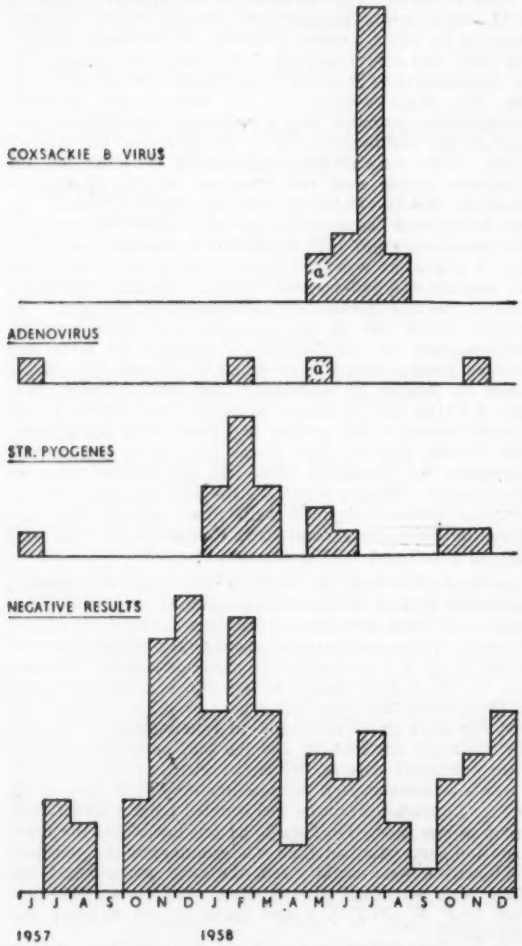
Case 2.—On July 21, 1958, a boy aged 11 suddenly developed pain in the right lower anterior chest, which was worse on deep breathing. He had moderate headache, nausea, sweating, and a poor appetite. His temperature rose to 99° F. (37.2° C.), and he slept poorly that night. The next day he felt at first slightly better, with less chest pain, but in the evening the temperature rose to 102.8° F. (39.3° C.) and the chest pain returned. On examination at the time the child did not look ill and the only abnormal physical sign was nasal catarrh, which in his case was habitual. There was neither neck stiffness nor abnormal signs in the chest. Coxsackie B3 virus was isolated from a throat swab taken at this time. On July 24 he felt better and the headache and chest pain had gone. On examination the palpebral conjunctivae were slightly red, the nose was blocked, but there were no other clinical signs. His temperature was then 99.5° F. (37.5° C.), and thereafter his recovery was uneventful.

Case 3.—On July 11, 1958, a girl aged 10 suddenly complained of headache, feverishness, and a slight soreness at the back of the nose. The next day she felt better but later developed a sore throat, shivered, and was found to have a temperature of 102° F. (38.9° C.). A slight cough and nasal symptoms followed and the moderately severe headache persisted. On examination the same day she did not appear very ill. She had a slight redness of the palpebral conjunctivae and red throat with some oedema. Her cervical lymph nodes were moderately enlarged and slightly tender. Her nose was blocked, but there were no abnormal signs in the chest and she had no neck stiffness. Coxsackie B3 virus was isolated from a throat swab. Her temperature fell gradually, and by the fifth day she felt quite fit. Examination at that time revealed a moderately red pharynx, with two greyish plaques, 2 mm. in diameter, on the soft palate, which was otherwise normal. *Family History*:—Her only sister had

a similar illness, with onset two days later. Coxsackie B3 virus was isolated from her throat swab. Her mother and father remained well.

Epidemiological Observations

The first two cases of Coxsackie infection occurred in the latter half of May, 1958—one in association with an adenovirus, type 4. From mid-June onwards cases were frequent, but the incidence appeared to be lessening before observations were interrupted in late August; no further isolations were made during the remaining period of the survey (see Chart). Therefore all Coxsackie virus



Monthly totals of viral and bacterial isolations. ☐ represents one case. ⧈ represents a double infection with adeno and Coxsackie B viruses.

isolations were made during a period of about 12 weeks, in which 20 out of 39 throat swabs examined were positive. During the last six weeks of this period, when Coxsackie virus was isolated from 12 of 20 patients, swabs were taken from the throats of 22 children who presented with illnesses other than febrile respiratory infections. These were tested for Coxsackie virus with negative results. There was thus a positive correlation between febrile respiratory illness and Coxsackie virus isolation.

During the epidemic there were 19 cases from which virus was not isolated. In most of these pharyngitis was the predominant clinical feature. No cases of meningeal involvement, other than that reported above, were seen among children or adults in the general practice.

Coxsackie virus was isolated from more than one individual in each of three families, the intervals between onset of the two illnesses being 0, 2, and 4 days respectively. A limited exposure to infection, from which the incubation period could be defined more precisely, was not observed, but the intervals given would be compatible with the usual incubation period, which is assumed to be from two to four days (Rhodes and Van Rooyen, 1958).

Fourteen families in which at least one isolation of Coxsackie B virus had been made were followed up. They totalled 65 individuals (30 adults and 35 children), of whom 4 adults and 20 children became ill. The attack rates based on clinical illness were therefore 13% and 57% respectively. In these families, 51 persons (30 adults and 21 children) were exposed to a primary case of Coxsackie B virus infection; 10 febrile illnesses occurred (four among adults and six among the children), indicating a secondary attack rate of 20%.

Adenovirus Isolations

Adenoviruses were isolated from children aged 1, 5, 6, and 8 years of age (types 2, 3, 1, and 4 respectively). These infections occurred at widely separated intervals (see Chart). The type 2 and type 3 infections were associated with a moderately severe illness with fever of five and four days' duration respectively, and both children had enlarged cervical glands and moderate inflammation of the throat; one of them also had a cough. Conjunctival redness was not more than that seen in many other upper respiratory infections. In the case from which type 1 virus was isolated, fever was observed to last only 24 hours. The patient had a moderately sore throat and headache, with a slight follicular exudate in the throat and tender cervical glands. In the case from which both a type 4 virus and Coxsackie B3 virus were recovered the illness started with sudden inflammation of the left eye, followed by involvement of the other eye. Oedema and follicle formation occurred in the lower palpebral sacs, with inflammation also over the bulbar conjunctivae. Slight changes in the throat, with fever, moderate cervical-gland enlargement, and pre-auricular-gland enlargement followed.

Bacterial Infections

The majority of *Str. pyogenes* isolations occurred during the period January to March, 1958, during which time 12 out of 41 swabs examined were positive. The predominant feature of the illness was pharyngitis, and, although the rest of the upper respiratory tract was usually involved to some extent, abnormal signs were not found in the chest. The throat changes were, on the whole, more severe than those seen in other infections during the survey. Follicular exudate occurred in the throats of one-third of the streptococcal cases, and tender, moderately enlarged upper anterior cervical glands were found in one half. Table II shows that most of the other clinical features were similar to those found in a group of undifferentiated respiratory infections.

Pneumococci were isolated in heavy culture from 25 cases occurring at irregular periods throughout the survey. There was thus no well-marked epidemic, and there was no consistency of type among eight strains tested (four of type II, one of type III, and three not of

types I, II, or III). In 7 out of 22 controls pneumococci were also found in heavy culture. Analysis of signs and symptoms did not show any distinctive clinical features in these infections. For these reasons we were unable to determine their aetiological significance.

Discussion

The number of respiratory illnesses recorded in our group of children was much lower than that found by Lidwell and Sommerville (1951) in a rural community, or that of Badger, Dingle, Feller, Hodges, Jordan, and Rammelkamp (1953) in a group of volunteer families. In those surveys, however, a regular inquiry was made week by week for the occurrence of respiratory infections. We relied upon our patients or their parents reporting illness to us when it appeared to them to require advice or treatment, and in our community it is probable that many of the less serious infections were not investigated.

In general an aetiological diagnosis of these illnesses could be deduced but seldom on clinical grounds alone. Table II shows that there were differences in the incidence of symptoms and signs between the groups of illness we were able to separate, but these differences could not be relied upon in any one case. Infection due to *Str. pyogenes* was correctly diagnosed most often, but cases occurred from which pneumococci, adenovirus or Coxsackie B3 virus were isolated when the clinical picture had suggested a streptococcal infection. Cases of myalgia were seen in the early part of the epidemic of Coxsackie B virus infections, and in some of these the diagnosis was confirmed by virus isolation. The clinical picture of a febrile pharyngitis associated with this agent became clear, however, only in retrospect.

Among the remainder of the illnesses a few fairly well defined syndromes could be discerned. Cases of febrile coryza and febrile bronchitis similar to those found in association with the haemadsorption myxoviruses by Parrott, Vargosko, Luckey, Kim, Cumming, and Chanock (1959) were not uncommon. Several cases of fever, lasting up to seven days, with enlargement of the cervical glands, but few other signs or symptoms suggesting glandular fever, were also seen. Short fevers with prominent constitutional symptoms and a rash resembling roseola infantum occurred from time to time throughout the survey. These observations suggest that further differentiation of acute respiratory illness on clinical grounds may yet be possible. Such advances will depend on the continued application of laboratory techniques to these problems.

Since their discovery by Dalldorf and Sickles (1948) Coxsackie viruses have been shown to be associated with a variety of clinical syndromes. In particular, Coxsackie B viruses have caused epidemic myalgia, aseptic meningitis, and mild pharyngitis. More recently they have been found to give rise to a severe and sometimes fatal myocarditis in infants (Javett, Heymann, Mundel, Pepler, Lurie, Gear, Measroch, and Kirsch, 1956). Infection with these viruses, which are usually only moderately severe, may thus be of considerable importance in a community, especially within the family.

During epidemic periods of Coxsackie infection the virus may be isolated from the faeces of many apparently healthy persons, particularly children. It may therefore sometimes be difficult to assess the aetiological significance of the presence of Coxsackie virus in the faeces of a clinical case. Virus is present in the throat probably for a short time only during illness. For this reason, and also because virus was not isolated from the throats of control children examined during the epidemic period, it seems likely that in those of our patients from whom virus was recovered it was the cause of the observed illness. This conclusion is supported by the occurrence of a fourfold rise of titre in the one patient from whom paired sera were tested for neutralizing antibodies.

Accounts of epidemics due to Coxsackie B virus have generally stressed the occurrence of one type of illness, either myalgic or meningeal (Warin, Davies, Sanders, and Vizoso, 1953 ; Rubin, Lehan, Doto, Chin, Heeren, Johnson, Wenner, and Furcolow, 1959). Gordon, Lennette, and Sandrock (1959), in a review of this subject, conclude that age may be a possible factor in determining the type of disease. At the same time they refer to the variety of clinical manifestations which may be present during an epidemic. Pharyngitis predominated in our own cases, which were similar to those described in a family outbreak by Jordan, Stevens, Katz, and Dingle (1956).

Our cases occurred at a time when Coxsackie B virus infections were prevalent in many parts of the country. In West Surrey this virus was isolated from a number of patients with an illness resembling non-paralytic poliomyelitis (Cook, 1959), though none of these came from the general practice investigated. Most of these patients were admitted to hospital with a moderately severe illness. Possibly the milder type of disease seen in our cases was more representative of the common response to infection with this virus.

In our survey the isolation rate for adenoviruses was similar to that found by Jordan, Badger, Curtiss, Dingle, Ginsberg, and Gold (1956). It is not clear whether such sporadic infections are responsible for the antibodies that are known to occur in young adults (Huebner, Rowe, Ward, Parrott, and Bell, 1954 ; Stovin, 1958), or whether these antibodies are mainly caused by recurrent epidemics and subclinical infections. Type 4 adenovirus is an unusual type to be encountered in childhood, as most isolations have been made in military populations. However, van der Veen and van der Ploeg (1958), in the Netherlands, described an outbreak of pharyngo-conjunctival fever in children, part of which was due to this type.

It is known that adenovirus types 1 and 2 are common latent viruses in young children. In the absence of tests for complement-fixing antibodies or of control studies, it is difficult to assess the aetiological significance of the four strains isolated.

Using a comparatively simple technique, we were able to isolate a potential pathogen in 28% of our cases. HeLa cells, however, are not suitable for the isolation of Coxsackie A viruses or for most of the haemadsorption myxoviruses such as cause acute respiratory disease in children. No doubt the proportion of illnesses identified as viral infections would have been higher if serological tests, stool culture, and a less restricted virological technique had been employed.

Summary

Acute respiratory infections occurring among children up to 18 years of age, in a general practice, were investigated by clinical, bacteriological, and virological methods. 146 illnesses were investigated among a group of 595 children over the period June 1, 1957, to December 31, 1958.

In 41 (28.1%) of the illnesses investigated, one or more pathogens were isolated from throat swabs.

Nineteen isolations of Coxsackie B3 virus and one of Coxsackie B4 virus were made over a period of 12 weeks during the summer of 1958. Most patients suffered from a febrile pharyngitis, but two myalgic and one mild meningeal illness also occurred. This epidemic coincided with an increased prevalence of Coxsackie B3 virus infection in West Surrey.

Four adenoviruses of types 1 to 4 inclusive were isolated, associated with three illnesses characterized by pharyngitis and lymphadenopathy and one by pharyngoconjunctivitis.

Str. pyogenes was isolated 18 times. Pharyngitis more severe than that seen in any other illnesses at the time, with some involvement of the upper respiratory tract, characterized these infections.

Though the frequency distribution of particular symptoms varies to some extent in the different infections, it is clear that in the individual patient a clinical diagnosis of the infecting agent cannot be made with certainty. Further knowledge of the aetiology of these upper respiratory infections can come about only by close collaboration of the medical practitioner with the laboratory.

During the investigation, typing of Coxsackie B viruses and adenoviruses was kindly carried out by Dr. A. J. H. Tomlinson, Bacteriological Laboratory, County Hall, London, and by the Virus Reference Laboratory, Colindale. We are also grateful to Dr. N. Richardson, Pathological Laboratory, Epsom District Hospital, for organizing facilities for storage and transport of frozen specimens; and to the Distillers Company Limited, Great Burgh, Epsom, for supplies of "cardice."

REFERENCES

Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., jun., and Rammelkamp, C. H., jun. (1953). *Amer. J. Hyg.*, **58**, 31.
Cook, G. T. (1959). *Monthly Bull. Minist. Hlth Lab. Serv.*, **18**, 138.
Dalldorf, G., and Sickles, G. M. (1948). *Science*, **108**, 61.
Gordon, R. B., Lennette, E. H., and Sandrock, R. S. (1959). *A.M.A. Arch. intern. Med.*, **103**, 63.
Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A. (1954). *New Engl. J. Med.*, **251**, 1077.
Javett, S. N. Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I. Gear, J., Measroch, V., and Kirsch, Z. (1956). *J. Pediat.*, **48**, 1.
Jordan, W. S., jun., Badger, G. F., Curtiss, C., Dingle, J. H., Ginsberg H. S., and Gold, E. (1956). *Amer. J. Hyg.*, **64**, 336.
—— Stevens, D., Katz, S., and Dingle, J. H. (1956). *New Engl. J. Med.*, **254**, 687.
Lidwell, O. M., and Sommerville, T. (1951). *J. Hyg. (Camb.)*, **49**, 365.
Logan, W. P. D., and Cushion, A. A. (1958). General Register Office: *Studies on Medical and Population Subjects*, No. 14: *Morbidity Statistics from General Practice*, vol. 1 (General). H.M.S.O., London.
Maxted, W. R. (1953). *J. clin. Path.*, **6**, 224.
Parrott, R. H., Vargosko, A., Luckey, A., Kim, H. W., Cumming, C., and Chanock, R. (1959). *New Engl. J. Med.*, **260**, 731.
Rhodes, A. J., and Van Rooyen, C. E. (1958). *Textbook of Virology*, 3rd ed. Baltimore.
Rubin, H., Lehan, P. H., Doto, I. L., Chin, T. D. Y., Heeren, R. H., Johnson, O., Wenner, H. A., and Furcolow, M. L. (1958). *New Engl. J. Med.*, **258**, 255.
Stovin, S. (1958). *J. Hyg. (Camb.)*, **56**, 404.
Veen, J. van der, and Ploeg, G. van der (1958). *Amer. J. Hyg.*, **68**, 95.
Warin, J. F., Davies, J. B. M., Sanders, F. K., and Vizoso, A. D. (1953). *Brit. med. J.*, **1**, 1345.

Requirements for Halsted's mosquito artery forceps (stainless steel, nominal overall length 4¼ in.) are specified in a new British Standard (B.S. 3246:1960). Copies of this standard may be obtained from the British Standards Institution, Sales Branch, 2, Park Street, London, W.1. Price 4s. (Postage extra to non-subscribers.)

IS UNIVERSAL VACCINATION AGAINST PERTUSSIS ALWAYS JUSTIFIED?

BY

JUSTUS STRÖM, M.D.

From the Hospital for Infectious Diseases, Stockholm, Sweden

Pertussis is still a great child-killer in many countries. Effective vaccines are now available, but are not devoid of risks, especially of a neurological nature. In some countries—for example, Sweden—the illness has assumed increasingly mild forms and the mortality is now very low. Thus the situation may arise when we must weigh up the relative advantages and disadvantages of vaccination.

There is no doubt that the new vaccines are very effective against pertussis. The British Medical Research Council reported in 1951 that cases of pertussis had been reduced to about one-fifth. Similar results are reported from the U.S.A. The new Swedish pertussis vaccine, which is given as a triple-vaccine (alum-precipitated) against diphtheria, tetanus, and whooping-cough, is prepared on modern principles (Arvidson and Ullberg-Olsson, 1952). It has good serological action (Ericsson *et al.*, 1952; Vahlquist *et al.*, 1954; Laurell *et al.*, 1957). The effect of its application to the community compares favourably with that produced by the best foreign vaccines (Rabo, 1956).

Neurological Complications after Pertussis Vaccination

The earliest report of neurological complications after pertussis vaccination came from Denmark (Madsen, 1933). Other isolated instances were published later, but the first really alarming report came from the U.S.A. when Byers and Moll (1948) described 15 severe cases; two of the patients died. All of those who recovered showed persistent convulsions, seven were mentally retarded, five had a hemiplegia, and two were blind. Toomey (1949) thereafter addressed a questionary to paediatricians in the U.S.A.; 54 answered and reported 38 cases of convulsions with 2 deaths and 12 irreversible cerebral lesions. In Switzerland, Köng (1953), who had himself observed one death and one case of convulsions accompanied by hemiplegia, reported 82 cases known up to 1951. Halpern and Halpern (1955) sent out a new questionary in the U.S.A., and received 56 replies reporting 15 cases of convulsions with one death and three irreversible lesions. Relatively speaking, the situation appeared to have improved, and this was attributed to the higher degree of purity of the vaccines.

In 1958 Berg reported on a personally observed case (convulsions and progressive dementia), which was the seventh from Great Britain. Berg collected data on 108 cases. Many different types of vaccine were implicated; the reactions might occur after any of a series of inoculations, but were more common after the first or second; the interval between vaccination and onset of reactions was usually brief. There were 15 deaths. Thursby-Pelham and Giles (1958) reported six cases (one of which had been included in Berg's series), Andrews (1958) two, and Leigh (1958) and Jones (1958) one each.

Soon after the introduction of triple vaccination on a large scale in Sweden in the mid-'fifties, suspect cases of severe vaccination reactions came to our knowledge. Consequently, at the end of 1958 a questionary was addressed to all 36 children's hospitals and to all 28

hospitals for infectious diseases; replies were received in every case. Subsequently questionaries were sent to 693 child-welfare centres asking for reports on unusual cases observed among out-patients. Replies were received from 559 (81%).

Neurological complications among in-patients during the years 1955–8 were reported in 18 cases. There were four deaths, two of which were sudden. One child was found dead in bed 20 minutes after the second injection; the other, six hours after the first inoculation. In the third fatal case the child developed fever and showed great anxiety after the second injection. Thereafter the child became comatose and later developed convulsions and paresis of the ocular muscles and left arm. Death occurred on the fifth day. Histological examination of the brain showed signs of an acute encephalitis with perivascular infiltration and demyelination. The fourth fatal case showed symptoms of mild rhinopharyngitis one day after the third injection. Severe convulsions developed on the fourth day, and the child died suddenly on the fifth day. In this case histological examination of the brain showed small ring haemorrhages and perivascular oedema with some cellular infiltration.

Of the 14 children who survived, three developed a decerebrate condition. The first of these was feverish, vomited, and had screaming fits for several days after the second inoculation. Thereafter there was progressive mental deterioration. The same acute condition, combined with convulsions, rigidity, conjugate deviation of the eyes, and nystagmus, came on in the second child after the first inoculation. The third case had fever for two to three days after the first injection and was listless for a week; after the second injection there was a similar reaction, but on this occasion it was followed by convulsions and rapid mental deterioration.

In the remaining 11 cases the predominant signs in the acute stage consisted of convulsions in six cases, stupor and coma in three, and collapse in one case. These signs developed from two to three hours after the injection up to five and seven days. The eleventh patient showed marked listlessness after the first two inoculations and increasing mental deterioration after the third. Five of these patients were fully restored to health. Mental retardation was seen in three patients, in one combined with cerebral palsy and deafness, and in another with cerebral palsy and epilepsy. In the remaining three patients epilepsy developed in one case immediately (a mongoloid child), in the others after one and three months.

Neurological complications among patients at the welfare centres were observed in two cases in 1955, in five cases in 1957, and in 11 cases in 1958, making 18 in all. Fifteen of these patients had convulsions, two became comatose, and one had a "collapse." Convulsions were reported in one case after all three injections and in another after two. Repeated attacks after one injection were seen in three patients. Fever was a usual symptom. The time interval in eight cases was 3–12 hours, in four cases 12–24 hours; one started to react on the second day and one on the fifth.

To summarize, a total of 36 children showed neurological manifestations. In 24 of these the initial symptom was convulsions, in six cases coma, and in four acute collapse. At least 11 and probably 13 children had signs indicative of an encephalopathy. Altogether there were four deaths. Of those who recovered, nine showed severe cerebral sequelae.

Comparison Between Neurological Complications after Pertussis and after Pertussis Vaccination

Byers and Moll (1948) reported 26 severe pertussis encephalopathies during 10 years at the hospital in Boston where their 15 examples of post-vaccination lesions were observed. It is unfortunate that these figures cannot be correlated with the incidence of the disease or the total number of vaccinations.

Some idea of the incidence of neurological reactions to pertussis can be obtained from material collected during the 10-year period 1948–57 from the 64 hospitals in Sweden previously mentioned. During those years 31 children with neurological complications to pertussis were treated in these hospitals. Of these children, two died and eight had severe sequelae with cerebral palsy, mental retardation, or epilepsy. A rough calculation shows that during this 10-year period about 725,000 children in Sweden had developed pertussis. During 1955–8 17 examples of cerebral complications after vaccination had been treated in the same hospitals. During the same period roughly 215,000 children had been vaccinated at the child-welfare centres.

With due reservation for the problems involved in diagnosis and in the collection of the material, and for the approximations in the calculation, it might be fair to say that in Sweden the incidence of neurological complications after pertussis does not appear to be as high as that after vaccination. The total incidence of neurological reactions after vaccination in the present series was 36 in a total of 215,000 vaccinated children, or about 1 in 6,000; death or permanent defect occurred in 13, or about 1 in 17,000.

Pertussis Morbidity and Mortality in Sweden

Reports of susceptibility to pertussis vary fairly considerably—Sako (1950) 80–90%, de Rudder (1934) 60–80%, Bradford (1952) 85–90%, Smillie (1952) 95%. A distinction should perhaps be made between "susceptibility to the infection" and the disease in its distinctive and manifest form. "Clinical whooping-cough"—that is to say, with typical attacks—accounts, according to Gordon and Hood (1951), for 75% of cases or above.

To assess the morbidity in Stockholm, I made a study of the records of 2,000 schoolchildren born in 1939 whose detailed clinical records were available up to 1951—that is, up to an age of 12 or 13 years. The number who had developed recognizable pertussis was 1,331 (65%). In the highest social class the figure was 69%, in the lowest 62%. Thus Stockholm seems to have a comparatively low morbidity.

The mortality from pertussis in Sweden, as in other countries, has dropped very greatly in recent years. Thus in the five-year period 1911–15 nearly 800 children died each year from pertussis, against only 10 in the period 1951–5. Indeed, even among infants the mortality is now very low. Among hospitalized patients in Stockholm, for example, the mortality during the period 1934–53 had fallen from 3.4% to zero (Jernelius, 1958).

The fall in mortality is undoubtedly due in large part to the general improvement in children's health and to the improvement in social and medical facilities. A similar reduction of mortality has taken place in other contagious diseases, such as measles and scarlet fever.

Survey of Neurological Reactions after Pertussis Vaccination

Adding to Berg's figure from 1958 the cases reported in Great Britain and in this study, the total of 153 cases is distributed as follows: U.S.A. 93, Sweden 36, U.K. 16, Denmark 2, Switzerland 2, Canada 2, France 1, Argentine 1. An analysis by type of vaccination, injection number, and time interval, so far as such data are available, gives the following figures. Vaccine—pertussis alone, 28; pertussis + diphtheria, 17; triple, 67. Injection—first 48, second 36, third 18, fourth 3. Time interval—first day 78, second 10, third 5, fourth and thereafter 11.

Discussion

It must at once be said that it is impossible to adduce strictly scientific evidence that vaccination was the responsible factor in all the cases in my series, any more than in earlier publications. In individual cases another genesis is conceivable, due to the chance of circumstances. None the less, in no case can the possibility of association with vaccination be denied. The time relationship with vaccination is strongly suggestive; the symptoms conform to the findings of other authors; and the effects are very similar to those seen in the neurological sequelae to pertussis.

The possibility of simultaneous viral infection of the central nervous system has been suggested; but in Sweden the most common viruses which cause meningitis (polio, Coxsackie, E.C.H.O., Russian spring-summer encephalitis) never present such syndromes. Moreover, such reactions have not been reported after other vaccinations performed on a large scale—as, for instance, against diphtheria or poliomyelitis.

It may be assumed that the neurological complications after whooping-cough and after vaccination are provoked by the same agent, so that whether or not a reaction occurs might depend on the individual disposition. This assumption might encourage one to adopt the view that the child who reacts so powerfully to the vaccine would be the child who would also have developed neurological symptoms in whooping-cough. This is, to say the least, a dangerous line of thought, for it is unlikely that the sudden administration of a large dose of vaccine can be compared with the course of the natural infection—an infection which might in some cases have been mild. In this context it is of interest that Pittman (1951) showed that the sensibility of experimental animals to histamine may be greatly increased by pertussis vaccines. On inhalation of *H. pertussis* a similar sensibility occurred, but more slowly and of longer duration.

If the use of triple vaccination is to be continued its hazards should be appreciated and certain contraindications emphasized. Unfortunately the reaction often follows the first injection, so that it is not always possible to foresee whether a reaction will occur. The rapidity with which the reaction appears seems to suggest the possibility of a toxic or allergic factor. Berg (1958) mentions seven cases which exhibited accentuated reactions after repeated inoculations, and such cases are also included in our own series. Halpern and Halpern (1955) also suggest a certain caution with respect to children with a history of other allergic manifestations. Köng (1953) considers that familial neurological diseases, a history of convulsions, allergy, poor general health, and acute infections should all be regarded as contraindications. Berg (1958) and Cockburn (1959) state that continued vaccination is absolutely contraindicated in any suggestion of a neurological reaction to a previous pertussis inoculation. I imagine that we all must agree with these proposals.

In most countries whooping-cough is still a serious illness with an appreciable mortality risk. The W.H.O. statistics for 1955 show for 28 countries a mortality of 18 per million inhabitants per annum; in Sweden the rate was 1 per million. Only 65% of children in Stockholm develop clinical whooping-cough. Therefore the disease no longer imposes the burden on the family which it has done in the past.

In the light of these circumstances the attitude to vaccination cannot be the same in all countries. When there is a risk, and when the neurological complications may either be fatal or lead to serious consequences for the individual and the family, the situation needs to be reconsidered. Thus it may be questioned whether universal vaccination against pertussis is always justified, especially in view of the increasingly mild nature of the disease and of the very small mortality. I am doubtful of its merits at least in Sweden, and I imagine that the same question may arise in some other countries. We should also remember that the modern infant must receive a large number of injections and that a reduction in their number would be a manifest advantage.

Summary

In Sweden, as in several other countries, neurological complications after pertussis (triple) vaccination have been observed. A nation-wide investigation showed that 36 cases of such complications had occurred in about 215,000 vaccinated children (1 in 6,000) during 1955–8. Most of these consisted of convulsions, coma, or collapse, and the children were restored to health; but there were four deaths, of which two were sudden, and nine cases indicative of encephalopathies with severe lesions (1 in 17,000). An investigation of the incidence of neurological complications after pertussis showed that this was not so high as after vaccination. The increasingly mild nature of whooping-cough and the very low mortality in this disease in Sweden makes it questionable whether universal vaccination against it is justified. The same question may perhaps arise in some other countries.

References

Andrews, J. N. H. (1958). *Brit. med. J.*, **2**, 385.
Arvidson, M., and Ullberg-Olsson, K. (1952). *Svenska Läk.-Tidn.*, **49**, 632.
Berg, J. M. (1958). *Brit. med. J.*, **2**, 24, 385.
Bradford, W. L. (1952). In *Bacterial and Mycotic Infections of Man*, edited by R. J. Dubos, 2nd ed., p. 536. Lippincott, Philadelphia.
Byers, R. K., and Moll, F. C. (1948). *Pediatrics*, **1**, 437.
Cockburn, W. C. (1959). *Brit. med. J.*, **1**, 1343.
Ericsson, H., Hesselvik, L., and Vahlquist, Bo. (1952). *Svenska Läk.-Tidn.*, **49**, 635.
Gordon, J. E., and Hood, R. I. (1951). *Amer. J. med. Sci.*, **222**, 333.
Halpern, S. R., and Halpern, D. (1955). *J. Pediat.*, **47**, 60.
Jernelius, H. (1958). *Acta Paediat. (Uppsala)*, **47**, 56.
Jones, P. (1958). *Brit. med. J.*, **2**, 860.
Köng, E. (1953). *Helv. paediat. Acta*, **8**, 90.
Laurell, G., Mellbin, T., Rabo, E., Vahlquist, B., and Zetterquist, P. (1957). *Klin. Wschr.*, **35**, 920.
Leigh, D. (1958). *Brit. med. J.*, **2**, 637.
Madsen, T. (1933). *J. Amer. med. Ass.*, **101**, 187.
Pittman, M. (1951). *J. infect. Dis.*, **89**, 300.
Rabo, E. (1956). *Svenska Läk.-Tidn.*, **53**, 509.
de Rudder, B. (1934). Cited by A. Grumbach, *Die Infektionskrankheiten und ihre Erreger*, 1958, p. 571. Thieme, Stuttgart.
Sako, W. S. (1950). Pullen: *Communicable Diseases*, p. 364. Lea and Febiger, Philadelphia.
Smillie, W. G. (1952). Cited by A. Grumbach, *Die Infektionskrankheiten und ihre Erreger*, 1958, p. 571. Thieme, Stuttgart.
Thursby-Pelham, D. C., and Giles, C. (1958). *Brit. med. J.*, **2**, 246.
Toomey, J. A. (1949). *J. Amer. med. Ass.*, **139**, 448.
Vahlquist, Bo., Ericsson, H., and Hesselvik, L. (1954). *Acta Paediat. (Uppsala)*, **43**, 15.

CLINICAL EXPERIENCE WITH NORETHISTERONE AND NORETHISTERONE ACETATE

BY

GEORGE L. FOSS, O.B.E., V.R.D., M.A., M.D.
Clinical Assistant to Endocrine Clinics, United Bristol Hospitals

The discovery of the 19-nortestosterone steroids had made available oral substances for clinical use with a more potent progestational effect than the natural hormone progesterone by injection. Previously, for many years the only oral progestogen was ethisterone—ethinyltestosterone, pregneninolone, or anhydrohydroxy progesterone—which was of low potency and about 12 to 15 times less effective than a daily injection of 20 mg. of progesterone for 14 days in producing a full secretory phase in the endometrium (Wied and Davis, 1958).

The relationship of these norsteroid progestogens to the naturally occurring hormone in the corpus luteum, and their uses, are discussed by Swyer (1959a).

During the last two and a half years experience has been gained with the use of norethisterone (" primolut-N ") and more recently with norethisterone acetate.

Norethisterone, when given orally in a total dose of 150–200 mg. over 10 days to oestrogen-primed castrated women, or women with secondary amenorrhoea, has been shown to produce a good secretory response in the endometrium (Hertz, Waite and Thomas, 1956; Ober, 1957; Kaiser, 1957; Pots, 1957; Swyer, 1959b). It is, in fact, more potent by this route than progesterone by daily intramuscular injection.

Norethisterone acetate was developed by Junkmann (1959), and a dose of 10–40 mg. over 10 days given to oestrogen-primed castrated women likewise produced a full secretory-phase endometrium (Pots, 1958). Although Swyer (1959b), found a dose of 40–80 mg. more certain in this respect, both authors agreed that it was about three more times potent than norethisterone in its effect on the secretory transformation of the endometrium. However, both steroids are of equivalent potency in decreasing oestrogen and pregnanediol excretion (Brown, Fotherby, and Loraine, 1960), and when used to suppress or postpone menstruation Swyer, Sebok, and Barns (1960) found that a larger dose of norethisterone acetate was required.

When the present trial started, although the progestational dose of norethisterone was reasonably settled and its value established clinically, it was necessary to determine the smallest doses for the effective control of dysfunctional bleeding, when given over many cycles, in order to reduce the cost of long-term treatment. Little was known of the clinical use and value of norethisterone acetate.

The objectives of the trial were: (1) to confirm the dose of norethisterone acetate which would develop an oestrogen-primed endometrium into a secretory phase; (2) to observe and compare the clinical effects of both steroids in the treatment of primary and secondary amenorrhoea, the control of dysfunctional menstrual bleeding, and, in a smaller group, the control of oligomenorrhoea and dysmenorrhoea; (3) to observe the effect of norethisterone acetate on the postponement of menstruation.

Material and Method

The 90 patients in this series were attending the hospital out-patient department or were seen in private practice, and had mostly been referred from gynaecologists. Thirty-four were given only norethisterone, 21 were given only norethisterone acetate, and the remaining 35 had been treated with both steroids at different times. Norethisterone was available in tablets of 5 mg., and norethisterone acetate in tablets of 2 mg.

A series of patients with long-standing amenorrhoea were given oestrogens for 18 days, using tablets of ethinyloestradiol, 0.1 mg. daily, " premarin," 1.25 mg. t.d.s., or intramuscular injections of oestradiol monobenzoate, 10 mg. every four days, according to their individual tolerance. After this, norethisterone acetate was given in doses of 2, 4, or 6 mg. daily for 10 days. In a smaller number of similar cases norethisterone was given in doses of 10–15 mg. daily for 6–10 days after oestrogen priming.

Endometrial biopsies were then carried out with the use of a Sharman curette, and one or two small strips were taken from the upper portion of the anterior wall of the uterus. These biopsies were taken between the 25th and 32nd days of the cycle as near as possible to the last day of progestogen treatment.

Most of the biopsy material was fixed in Bouin's solution at once, except for some which was put into absolute alcohol as suggested by Pots (1959, personal communication), However, this method was abandoned owing to the degree of desiccation with distortion of the endometrium. Sections were stained with haematoxylin and eosin.

Interpretation of the degrees of secretory activity of the endometrium was based on descriptions by Rock and Bartlett (1937) and Swyer (1959c), taking into account study of the glands, nuclei, secretory activity, and also the state of the stroma, the tortuosity of the arterioles, and presence of venous lakes.

Most of the married patients with dysfunctional menstruation, with irregular or regular heavy or prolonged loss, had been previously curetted, but in some of the younger patients biopsies were not conducted to confirm a presumptive diagnosis of metropathia from the typical history. Some cases with menorrhagia were found to have cervical erosions or polyps or thought to have small fibroids, and were treated as a temporary measure before operation.

In a number of cases of menometrorrhagia with proved metropathia biopsies were made usually after 10 days' treatment with norethisterone acetate in different doses, and in some cases two or three biopsies were done in the same patient at intervals after various doses.

As a method of treatment it was usual to give norethisterone for 3 to 10 days from the 24th or the 18th day after the onset of a previous period; but with norethisterone acetate the dose was given as a rule for the last 10 days of the cycle.

Another scheme adopted in some cases of menorrhagia and dysmenorrhoea was that described by Swyer (1960) from the 5th to the 25th day, although this is more expensive. In a few cases norethisterone acetate has been given for 20 to 30 days after the 11th to the 23rd day to observe the effect on postponement of menstruation (Greenblatt, 1958).

In patients with primary amenorrhoea norethisterone was given cyclically in conjunction with oral oestrogens or implanted oestradiol tablets.

Both steroids were used in cases of secondary amenorrhoea, usually after oestrogen priming in the first half of the cycle, or were given together for 6 to 14 days cyclically. The number of patients, the cycles treated, and the indications are shown for both norethisterone and norethisterone acetate (Table I).

TABLE I.—*Number of Patients Treated*

Norethisterone	No. of Patients	No. of Cycles	Norethisterone Acetate	No. of Patients	No. of Cycles
Menorrhagia ..	26	101	Menorrhagia ..	38	205
Primary amenorrhoea	7	76	Secondary amenorrhoea ..	10	22
Secondary amenorrhoea ..	25	320	Others	8	20
Oligomenorrhoea ..	5	23			
Dysmenorrhoea ..	6	15			
Total ..	69	535	Total ..	56	247

Results

Amenorrhoea

Norethisterone was given to 25 patients in 320 cycles for secondary amenorrhoea, and to 7 patients in 76 cycles for primary amenorrhoea, with satisfactory regular cyclical rhythm. After an oestradiol implant cyclical norethisterone treatment ensured a regular shedding of the endometrium.

Three of the cases of secondary amenorrhoea were shown to have a slow-growing intrasellar tumour without any evidence of pressure on the optic chiasma, and with no other evidence of endocrine dysfunction except the failure of pituitary ovarian rhythm. In these, vaginal smears showed some oestrogenic activity, and cyclical bleeding occurred after the administration of norethisterone alone without any oestrogens.

Norethisterone acetate was given to only 10 patients with secondary amenorrhoea for 22 cycles. Various doses were used after the initial oestrogen priming, and biopsies were conducted in 12 of these cycles. Some of these cases were also given norethisterone to compare their secretory effect on the endometrium.

In these 12 biopsies after norethisterone acetate a secretory phase was observed in the endometrium in all of them except one. This varied in degree from minimal or early after doses of 20 mg. in 10 days (Figs. 1, 2, and 3) to moderate or full after total doses of 60 mg. The one exception was found in a patient who was unable to take ethinyloestradiol 0.1 mg. daily, and was given only two injections of oestradiol monobenzoate 10 mg. followed by 40 mg. of norethisterone acetate (Table II).

TABLE II.—*Cases of Secondary Amenorrhoea*

Case No.	Dose (mg.)	Biopsy Day	Result
			Norethisterone Acetate
1. Ar	40	28	Early secretory; nuclear migration; zona pellucida
2. Au	60	30	Secretory
3. H	60	28	"
4. H	40	32	No secretory phase. Inadequate priming with oestradiol benzoate
5. H	20	31	Slight secretory with active stromal reaction
6. Lo	40	30	Moderate secretory
7. Lo	60	28	Secretory
8. P	32	25	Early secretory with nuclear migration
9. T	20	28	Early secretory
10. T	40	28	Secretory with active stromal reaction
11. W	60	27	Moderate secretory
12. W	20	28	Minimal secretory; nuclear migration; stromal reaction
			Norethisterone
13. Ar	50	28	No secretory activity
14. Lo	100	28	Secretory
15. P	100	28	Early secretory
16. S	120	30	Moderate "

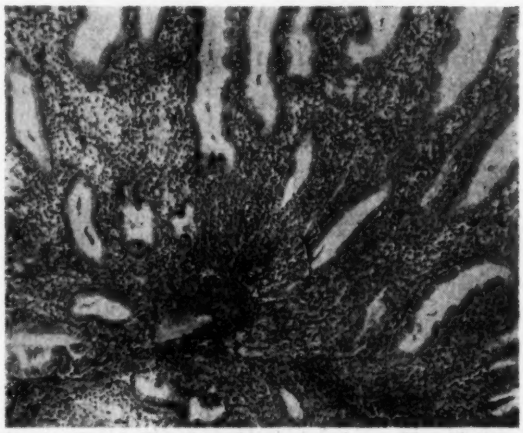


FIG. 1.—Case 9 (T). Secondary amenorrhoea. Norethisterone acetate 20 mg. in 10 days. Biopsy 28th day. (×94.) Early secretory phase.

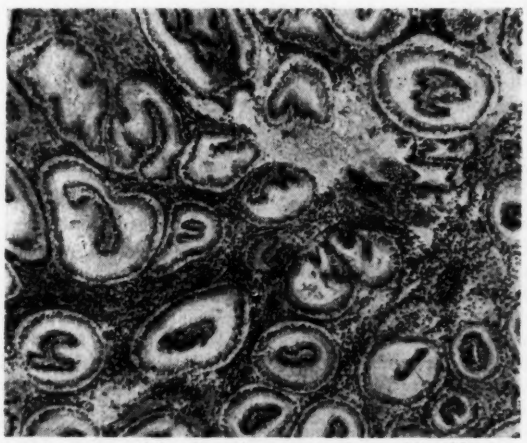


FIG. 2.—Case 1 (Ar). Secondary amenorrhoea. Norethisterone acetate 40 mg. in 10 days. Biopsy 28th day. (×94.) Early secretory activity with nuclear migration and zona pellucida.

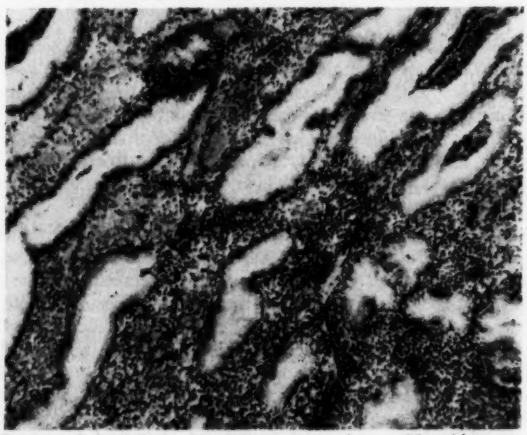


FIG. 3.—Case 7 (Lo). Secondary amenorrhoea. Norethisterone acetate 60 mg. in 10 days. Biopsy 28th day. (×94.) Secretory phase.

Only four patients were biopsied after norethisterone (Table II). Some degree of secretory activity was seen with 100 mg. In one woman, aged 29, a comparable secretory-phase endometrium was seen after 100 mg. of norethisterone and 40 mg. of norethisterone acetate. Previous treatment had been given before both of these cycles when the biopsy was taken.

Menometrorrhagia

There were 18 cases of metropathia treated with norethisterone acetate: of these, six were not proved by biopsy but had a typical history. Nine of the proved cases were given various doses over a 10-day period, and then had biopsies on the last day of treatment. The results are shown in Table III. It will be seen that in 18 out of the 20 cycles investigated treatment was given for 10 days prior to the biopsy as near as possible to the 28th day of the cycle, and with doses varying from 20 to 180 mg. a secretory change was found in all, although it was early or minimal in a few (Figs. 4, 5, and 6). Two biopsies were preceded by treatment with 2 and 6 mg. daily for 20 days from the 5th to the 25th day, and in both these endometria the glands were small and undeveloped, suggesting that ovulation had been suppressed (Fig. 7).

Bleeding immediately after this series of biopsies was normal except in three patients who had a heavy loss from a secretory-phase endometrium.

TABLE III.—*Cases of Metropathia Treated with Norethisterone Acetate*

Name	Dose (mg.)	Cycle Days	Biopsy Day	Result	Cycle Length	Loss
Ab	60	Last 10	26	Secretory; oedema; pseudodecidua	29	N
	40	,, ,,	31	Secretory with bleeding	32	N
Co	40	,, ,,	28	Secretory	28	N
El	60	,, ,,	23	,,	24	Heavy
	180	,, ,,	25	,,	27	N
	40	,, ,,	25	,,	25	N
	20	,, ,,	25	Early secretory	25	N
Fo	120	,, ,,	29	Secretory	30	Heavy
Ha	40	,, ,,	32	Early secretory	33	N
Sm	60	,, ,,	30	,, ,,	32	N
	40	,, ,,	28	,, ,,	29	N
	120	5–25	25	Small undeveloped glands	26	N
Wa	60	Last 10	26	Secretory; oedema; pseudodecidua	26	Scanty
Je	60	,, ,,	36	Secretory	38	N
Kr	60	,, ,,	30	Early secretory	32	N
	40	,, ,,	26	,, ,,	28	N
	20	,, ,,	25	Minimal secretory	26	N
No	60	,, ,,	34	Early secretory; oedema	36	Scanty
	40	5–25	32	Small undeveloped glands	33	Spots
Pi	60	Last 10	40	Early secretory	41	Heavy

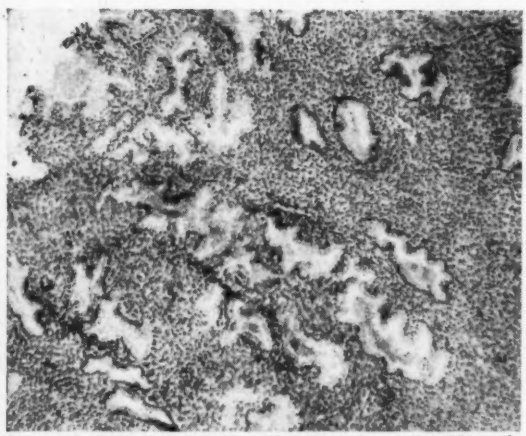


FIG. 4.—Case El. Metropathia. Norethisterone acetate 20 mg. in 10 days. Biopsy on 25th day. (×94.) Early secretory activity.

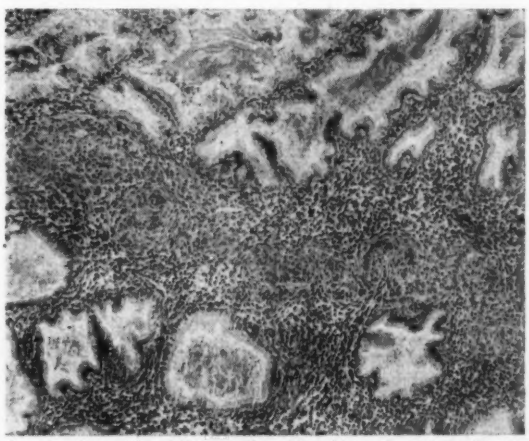


FIG. 6.—Case Ab. Metropathia. Norethisterone acetate 60 mg. in 10 days. Biopsy on 26th day. (×94.) Full secretory change with arterial tortuosity.

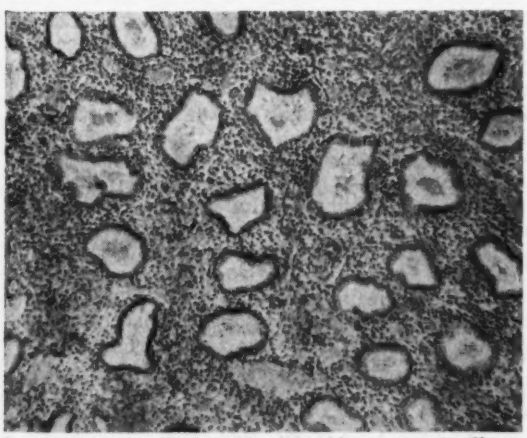


FIG. 5.—Case Sm. Metropathia. Norethisterone acetate 60 mg. in 10 days. Biopsy on 30th day. (×94.) Secretory activity with prominent arterioles.

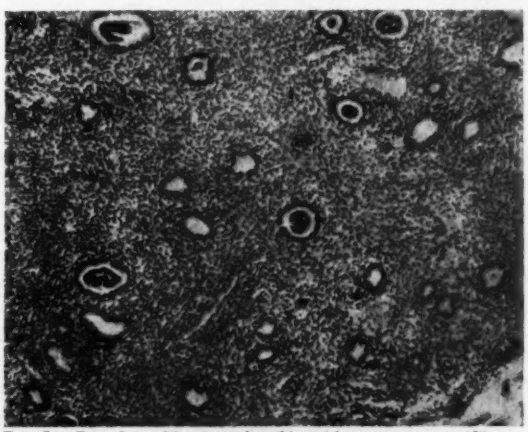


FIG. 7.—Case Sm. Metropathia. Norethisterone acetate 120 mg. from 5 to 25 days. Biopsy on 25th day. (×94.) Small inactive glands.

In the whole group of 38 cases of menometrorrhagia treated with norethisterone acetate, control of menstrual loss was obtained in 75% of 205 cycles, but the dose necessary to gain control varied from 20 to 320 mg. per cycle. The generally adopted dose was 60 mg. in the last 10 days. Fig. 8 shows the relationship of controlled to uncontrolled cycles for each dose level used. Fig. 9 shows the onset of bleeding relative to the end of treatment expressed as a percentage of treated cycles.

With norethisterone 26 patients were treated for 101 cycles with satisfactory control of menstrual loss in 83%. An average dose used was 90–150 mg., but control was sometimes achieved with as little as 10 mg. for four days or 15 mg. for three days after several cycles had been treated. Fig. 10 shows the relationship of controlled to uncontrolled cycles at each dose level.

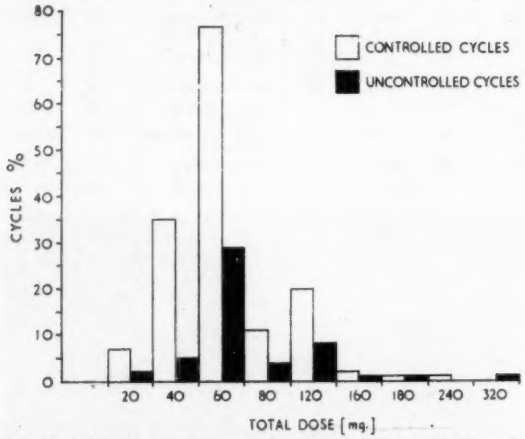


FIG. 8.—Treatment of menometrorrhagia with norethisterone acetate. White columns=controlled cycles; black columns=uncontrolled cycles.

FIG. 9.—Onset of bleeding relative to completion of course of norethisterone acetate in cases of menometrorrhagia. Showing percentage of treated cycles.

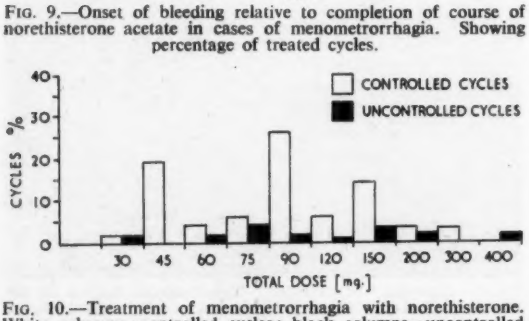


FIG. 10.—Treatment of menometrorrhagia with norethisterone. White columns=controlled cycles; black columns=uncontrolled cycles.

Haemostasis.—Some patients were first treated for very heavy and prolonged flooding, and in six such cases bleeding stopped after about 24–48 hours, and a normal withdrawal bleed occurred after finishing treatment. Cyclical treatment with either steroid was then continued.

Two patients with regular menorrhagia and one with metrorrhagia due to metropathia became pregnant during cyclical treatment with norethisterone acetate, and two of these, one in each group, gave birth to normal babies. The patient with metropathia had been trying to have a child for five years before treatment started.

The rest of the cases treated in this trial were made up of dysmenorrhoea, oligomenorrhoea, endometriosis, premenstrual tension, or premenstrual asthma, but the numbers in each group and the cycles treated are too few for a satisfactory clinical assessment of the value of the treatment. In several cases in this series treated during the last 10 days of the cycle painful menstruation was noted where it was normally unusual.

On 11 occasions treatment with norethisterone acetate was given from the 10th to the 23rd day of the cycle for 20 to 30 days, to determine whether menstruation could be postponed. This was successful only five times, when the cycle was longer than normal. In all except two a scanty breakthrough bleeding occurred before completion of the course (Table IV).

TABLE IV.—*Attempt to Postpone Menses by Norethisterone Acetate*

Patient	Starting	Dose mg. days	Result
Mo	19th day	4×30	Failed. Scanty bleed 31st day
Ma	21st ,,	6×28	,, Bled 29th day
,,	18th ,,	12×28	*Postponed.* Bled 34th day
Da	17th ,,	6×30	,, *to 49th day*
Wi	18th ,,	6×20	Scanty bleed on 29th day
,,	10th ,,	4×20	,, loss on 24th ,,
Kr	21st ,,	4×20	*Postponed to 42nd day*
Wa	21st ,,	6×20	Scanty bleed 30th day
Wi	18th ,,	16×20	Dribbling bleed 30th day
Bu	21st ,,	8×30	*Postponed to 37 days*
El	23rd ,,	4×30	,, ,, 50 ,,

Discussion

The results of these trials of norethisterone acetate on the oestrogen-primed endometria of cases of secondary amenorrhoea tend to confirm Swyer's (1959b) findings that an adequate secretory dose is slightly higher than that reported by Pots (1958). Although some evidence of secretory changes were seen with 20 mg., even 60 mg. in 10 days did not always produce a full secretory phase. Whereas in the few patients who had biopsies after treatment with norethisterone 100 mg. seemed to be a satisfactory transformation dose, which agrees with Pots's (1958) findings, a similar degree of transformation would appear to be 40–60 mg. of the acetate: so that the ratio is just about 2½–2:1. The difference in potency is probably too small to justify its introduction as an additional progestogen for clinical use, as norethisterone is already being successfully employed, with all its advantages over intramuscular progestogenic treatment. In the routine treatment of amenorrhoeas, both primary and secondary, or for long or irregular cycles with normal loss, both steroids are equally effective.

In dysfunctional heavy or prolonged menstruation, particularly when this is due to metropathia, both substances are again equally useful for controlling menstrual loss in about 75–83% of cases, which agrees well with the findings of Bishop and de Almeida (1960) for norethisterone.

Both steroids will regularize the cycles if an adequate dose has been given, and in the majority of cycles treated bleeding started within four days of finishing a course of treatment.

The endometrium of proved cases of metropathia was shown to have some secretory transformation even with 20 mg. of norethisterone acetate in 10 days, and subsequent bleeding was normal after biopsy in the majority, although occasionally a heavy menstrual loss followed a proved secretory transformation. A cyclical dose of 40–60 mg. of norethisterone acetate in 10 days or 90–120 mg. of norethisterone in the last phase of the cycle is generally satisfactory in producing regular normal bleeding, and is preferable, particularly in women who desire pregnancy. It also requires less steroid than if given from the 5th to the 25th day, and with the latter regime sometimes a breakthrough bleeding occurs before the patient has finished the 20 days' treatment, thus altering the cyclical rhythm.

A number of these patients treated for menorrhagia with cyclical progestogens at the end of the cycle complained of dysmenorrhoea, but, as Bishop and de Almeida (1960) found in their series, this was not severe enough to make them unwilling to continue treatment if the loss was successfully controlled.

Swyer's (1960) method of giving treatment for 20 days from the 5th to the 25th day of the cycle is more expensive, but has the advantage of inhibiting ovulation and so preventing dysmenorrhoea and acting as an oral contraceptive.

The number of cycles in this series when norethisterone acetate was given deliberately to attempt to postpone menstruation is small, partly because the quantity of this steroid available was not unlimited; but doses of up to 16 mg. daily for 20 to 30 days cannot be relied upon for this purpose. In this respect Swyer, Sebok, and Barns (1960) have shown that norethisterone acetate is less potent than norethisterone, of which 20–30 mg. daily will delay a normal menstrual period and induce a pseudo-pregnancy of as much as seven months (Greenblatt and Jungck, 1958).

Summary

During the last two and a half years norethisterone and more recently norethisterone acetate have been used in a total series of 90 women. Some were given either the one or the other, and some were treated with both steroids at different times. The conditions treated were primary and secondary amenorrhoea, oligomenorrhoea, some dysmenorrhoea, and a larger series of cases of menometrorrhagia.

For secondary amenorrhoea both steroids were equally effective when used with oestrogens to induce menstruation.

An assessment of the secretory transitional dose of norethisterone acetate in oestrogen-primed married women with secondary amenorrhoea was made, and the effect of similar doses on the endometrium of women suffering from metropathia was investigated.

The control of prolonged excessive regular or irregular menstruation was about equally effective with norethisterone and norethisterone acetate (83:75%), but, weight for weight, the latter was about twice as potent.

I am much indebted to Mr. H. L. Shepherd, Mr. S. D. Loxton, and Mrs. D. Bennett for allowing me to treat their patients and to publish these results; to Dr. A. L. Taylor for the pathological reports; to Professor T. F. Hewer for facilities for photomicrography; and to Dr. Jürgen Friebel, of Schering A.G., for supplies of norethisterone (primolut-N) and norethisterone acetate.

References

Bishop, P. M. F., and de Almeida, J. C. C. (1960). *Brit. med. J.*, **1**, 1103.
Brown, J. B., Fotherby, K., and Loraine, J. A. (1960). *Proc. roy. Soc. Med.*, **53**, 431.
Greenblatt, R. B. (1958). *Amer. J. Obstet. Gynec.*, **76**, 626.
—— and Jungck, E. C. (1958). *J. Amer. med. Ass.*, **166**, 1461.
Hertz, R., Waite, J. H., and Thomas, L. B. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 418.
Junkmann, K. (1959). *Proc. 15th Gen. Assembly Jap. Med. Congr., Tokio*, **1**, 697.
Kaiser, R. (1957). *Geburtsh. u. Frauenheilk.*, **17**, 24.
Ober, K. (1957). Academic Meeting of Gynaecologists, Basle.
Pots, P. (1957). *Zbl. Gynäk.*, **79**, 529.
—— (1958). *Klin. Wschr.*, **36**, 824.
Rock, J., and Bartlett, M. K. (1937). *J. Amer. med. Ass.*, **108**, 2022.
Swyer, G. I. M. (1959a). *Practitioner*, **183**, 211.
—— (1959b). *J. Endocr*, **18**, v.
—— (1959c). *Proc. roy. Soc. Med.*, **52**, 515.
—— (1960). *Brit. med. J.*, **1**, 121.
—— Sebok, L., and Barns, D. F. (1960). *Proc. roy. Soc. Med.*, **53**, 435.
Wied, G. L., and Davis, M. E. (1958). *Ann. N.Y. Acad. Sci.*, **71**, 599.

TREATMENT OF URINARY INFECTIONS WITH CYCLOSERINE

BY

R. W. FAIRBROTHER, T.D., M.D., D.Sc. F.R.C.P.
Director

AND

G. GARRETT, M.D., Dip.Path.*
Senior Registrar

Department of Clinical Pathology, Manchester Royal Infirmary

Infections of the urinary tract constitute one of the most difficult groups of infection encountered in a general hospital at the present time. Many are complicated by some underlying anatomical abnormality or neurological condition, and while infections with sensitive organisms, such as the coliforms, tend to respond readily to routine therapy, an increasing number are being caused by organisms resistant to the usual chemotherapeutic agents. The causative organism is often a *Proteus*, *Ps. pyocyanea*, or paracolon which tend to be resistant to the sulphonamides, nitrofurantoin, chloramphenicol, and tetracycline. These cases have consequently become a major problem, and the introduction of a new effective antibiotic would be an important development.

Cycloserine, an antibiotic prepared from *Str. orchidaceus*, was originally used for the treatment of tuberculosis. It has, however, a wide antibacterial spectrum, and, though it has a relatively low grade of *in vitro* activity, it has been found to produce concentrations in the urine which may be effective against some resistant organisms responsible for urinary infections (Welch *et al.*, 1955). Although toxic manifestations were a serious problem when cycloserine was used for the treatment of tuberculosis, only minimal side-effects were observed with the smaller doses required for urinary infections. Moreover, encouraging results were given in some patients with chronic resistant infections (Herrold *et al.*, 1955).

*Now Consultant Pathologist, Oldham.

It was therefore decided to carry out a trial of cycloserine in the treatment of refractory urinary infections—that is, those caused by organisms found to be resistant to, and/or had not responded to treatment with, the usual agents.

Methods

The sensitivity of the organisms, freshly isolated from the urinary infections, and the levels of cycloserine in urine were determined by the serial dilution technique. A stock solution in sterile distilled water was prepared with a special salt of cycloserine to give a final concentration of 10,000 μg./ml. Suitable doubling dilutions were made with special assay broth containing glucose and an indicator; 0.5 ml. was the volume used. In all cases the bacterial inoculum was 0.02 ml. of an undiluted overnight broth culture. Readings were taken after overnight incubation (usually 18 hours) at 37° C.; visible inhibition of growth was the criterion on which the results were based.

The urine was passed through a Seitz filter, after the bacteriological examination, for the determination of the cycloserine levels; dilutions were made with the special broth. Only the first and last specimens from female patients were collected by catheter; clean or mid-stream specimens, collected daily, were used for the other investigations. In each series a control set of dilutions of the standard cycloserine solution was prepared and all tubes received the standard inoculum (0.02 ml.) of the test organism, which was a relatively sensitive strain of *Staph. aureus*.

The blood levels were determined by a modification of the chemical technique described by Jones (1956).

Results

Various observations were made during the investigation, and the results are presented in four parts: (1) sensitivity *in vitro* to cycloserine of urinary pathogens, (2) blood and urine levels obtained after various schemes of dosage, (3) clinical results, and (4) development of resistance by the organisms *in vivo* and *in vitro*.

In Vitro Sensitivity Tests

A wide range of organisms isolated from simple and complicated urinary infections were subjected to routine testing (Table I).

TABLE I.—*In Vitro Activity of Cycloserine. Minimal Inhibitory Concentration on Urinary Pathogens (μg./ml.)*

Organism	No. Tested	μg./ml.					
		1,280	640	320	160	80	40
E. coli	107	2	8	45	50	2	—
Proteus	71	15	48	8	—	—	—
Str. faecalis	34	—	7	24	3	—	—
Ps. pyocyanea ..	30	3	17	10	—	—	—
Staph. albus	30	—	—	5	2	7	16
Staph. aureus ..	20	—	—	3	2	7	8
Paracolon strains ..	25	—	4	9	11	1	—
Aerogenes „ ..	17	—	6	7	4	—	—
Total ..	334	20	90	111	72	17	24

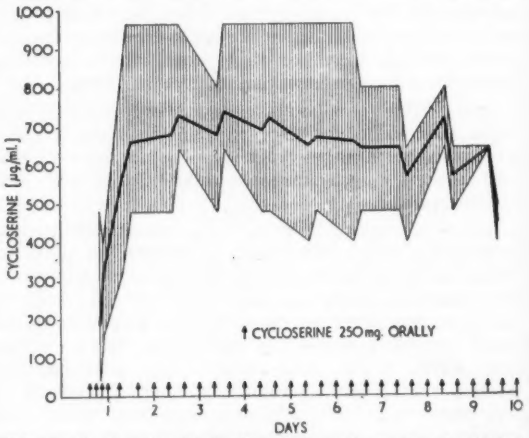
Cycloserine did not prove to be a very active antibiotic. Only 113 out of 334 organisms were inhibited by concentrations of 160 or less μg./ml.; these organisms were principally staphylococci and coliforms. Out of 334 organisms 110 were inhibited only by 640 or more μg./ml.; these were mainly strains of *Proteus* or *Pseudomonas* which are frequently responsible for obstinate urinary infections.

Blood and Urine Levels

Cycloserine was given orally to the first four patients in the following dosage: 250 mg. (one pulvule) statim, with 250 mg. after three hours and then 250 mg. at six-hourly intervals. In an attempt to obtain higher levels more quickly, the remainder received the 250-mg. dose at once, after intervals of three, six, and nine hours, and then six-hourly throughout the course of 5–10 days (average 7 days). The maximum total dosage was 10 g. Blood and urine estimations were usually made on samples collected during the morning, four hours after the previous dose of cycloserine, and in the afternoon two hours after the dose.

The blood levels were low; a range of 13–15 μg./ml. was soon reached, and levels of 19–27 μg./ml. were maintained.

Cycloserine is greatly concentrated in the urine, and much higher levels were obtained than in the blood; these tended to be consistent and also to remain steady throughout the course (see Chart). Levels of 960 μg./ml. were attained in 10 out of 21 cases, while in all cases a level of at least 400 μg./ml. was reached, being maintained throughout the course.



Urine levels of cycloserine in 22 patients under treatment. Shaded area is range of results, and the line is the average result. (One case was treated for 2½ days, one for 4 days, ten for 5 days, two for 6 days, four for 7 days, two for 8 days, and two for 10 days.)

Clinical Results

A total of 22 cases (14 males) were treated with cycloserine, and of these 17 were complicated by neurological or anatomical disorders. Of the uncomplicated cases, four were infected with *E. coli* and one with *Ps. pyocyanea*. Two of five uncomplicated but only 3 of 17 complicated cases had not received any previous treatment for the infection; 20 of the 22 patients received treatment for at least five days, four for seven days, and two for 10 days.

The drug was well tolerated by most patients. One patient, however, became incoherent and incontinent after 55 hours' therapy but rapidly recovered on withdrawal of the drug. Three others also showed definite side-effects, after 4 g. in two cases and 5 g. in the other; these were mainly undue drowsiness and dizziness, and were intensive enough to warrant cessation of the drug. Recovery was rapid and complete.

The clinical response varied greatly and the results have been divided into four separate grades: (1) com-

plete clinical and bacteriological cure; (2) temporary cure—relapse within 48 hours after cessation of treatment; (3) some clinical improvement but the urine never freed of organisms; and (4) no obvious effect—clinical or bacteriological.

The results have been so graded in relation to the nature of the infecting organism or organisms. Only 21 cases have been included, and four of them had a mixed infection (Table II).

TABLE II.—*Urinary Infections. Results of Treatment with Cycloserine (21 Cases with 26 Organisms)*

Organism	No. Isolated	Pre-treatment: M.I.C. μg./ml.	Grade of Response			
			1	2	3	4
E. coli ..	5	320	1*	2		1
	4	160	1	2		
			2			
Proteus ..	7	640		2	2	3
	2	320				2
Ps. pyocyanea	1	1,280			1	
	3	640				3
	1	320			1	
Str. faecalis	2	640	1*		1	
	1	320	1*			

* Mixed infection with bacteriological clearance only.
M.I.C. = Minimum inhibitory concentration.

Only three complete cures were obtained, and in each case the causative organism was a coliform with a relatively wide range of sensitivity to the antibiotics. Two of these cases were uncomplicated; the other was a case of tabes dorsalis with tidal drainage. Two other uncomplicated cases, infected with *E. coli*, showed only temporary improvement, and the fifth case was infected with a resistant strain of *Ps. pyocyanea*. In two cases of mixed infection the sensitive organisms were eliminated but the resistant organisms persisted.

In 6 out of 21 cases there was temporary improvement, with relapse at the end of treatment; four of these were caused by coliforms and two by *Proteus* strains. In 12 out of 21 cases there was little or no response. The 16 complicated cases included four in an advanced stage of disseminated sclerosis, two with tumours of the spinal cord and paralysis, while two had had operations for carcinoma of the bladder.

These results, though disappointing, were not unexpected, as we were deliberately dealing with unpromising material. The *in vitro* tests had, moreover, indicated quite clearly that in the majority of cases the urinary levels of cycloserine were unlikely to have any appreciable effect, particularly on the difficult *Pseudomonas* and *Proteus* strains.

Development of Increased Resistance to Cycloserine

The capacity of urinary pathogens to habituate themselves to cycloserine was examined under *in vitro* and *in vivo* conditions.

For the *in vitro* tests, various organisms were subcultured in broth containing increasing subinhibitory concentrations of the antibiotic, and were subjected to sensitivity tests. Some increase in resistance was found in all the organisms examined. While strains of *E. coli* did not readily develop increased resistance, *Aerogenes* strains showed an eightfold increase after four or five subcultures. An eightfold increase in resistance was produced by three out of three strains of *Ps. pyocyanea* in four subcultures and by three out of three strains of *Proteus* in five subcultures.

Resistance did not readily develop during routine treatment. Nevertheless, some increase was given by all strains examined, although it was usually only twofold. This was, however, sufficient in some cases to render such borderline organisms as *Proteus* and *Ps. pyocyanea* resistant to the antibiotic concentrations found in the urine.

Discussion

Disappointing results were obtained from the use of cycloserine in the treatment of stubborn urinary infections, most of which were selected for trial because they had failed to respond to the usual chemotherapeutic agents and were presenting a serious problem. Toxic symptoms, such as vertigo and drowsiness, were observed in 4 out of 22 patients (18%), and these were severe enough to warrant the withdrawal of the antibiotic. Recovery from these side-effects was, however, rapid and complete.

Clinical and bacteriological recovery from the urinary infection was produced in only 3 out of the 21 patients in the series. Two of these infections were uncomplicated and followed catheterization. *E. coli* was the causative organism of these three infections, and in each case it was sensitive to most of the usual chemotherapeutic agents, which would probably have proved equally effective. Although cycloserine is undoubtedly effective in coliform infections (Murdoch *et al.*, 1959), it cannot be recommended as a first choice in view of the risk of side-effects and the number of other possible active agents, including the sulphonamides.

The other 18 cases showed only temporary or no improvement; most of these were difficult and complicated cases, caused by resistant strains of *Proteus* and *Pseudomonas*.

The results, although disappointing, were not surprising. *In vitro* tests had shown that many strains of *Proteus* and *Ps. pyocyanea* are inhibited only by at least 640 μg./ml., while the maximum level demonstrated in the urine during therapy was 960 μg./ml. It is, however, possible that slightly higher levels might have been produced for short periods during the course. Nevertheless, under such conditions, cycloserine was unlikely to be effective.

There was no marked development of resistance by the causative organisms during the treatment, but any slight increase was sufficient to take some of the doubtful organisms out of the therapeutic range. When such a change in resistance was observed treatment was stopped before the full course was completed. It was considered that under such conditions continued therapy would almost certainly be ineffective, and would, moreover, expose the patient to the risk of side-effects.

These results indicate clearly that if cycloserine is to be used for the treatment of urinary infections it is desirable, if not essential, to have adequate laboratory control, particularly the isolation and sensitivity-testing of the causative organisms and the determination of urinary levels during treatment. With such control, the cases likely to respond to treatment can be selected and any unnecessary risk of toxic reactions avoided.

Summary

Twenty-two cases of urinary infection were treated with cycloserine. Side-effects, warranting cessation of the drug, were experienced by four patients.

Three infections with *E. coli*, which proved to be a relatively sensitive organism, were eradicated.

The response of the other infections, usually complicated and due to such resistant organisms as *Proteus* and *Ps. pyocyanea*, was disappointing. Temporary improvement was experienced by 6 out of 21 patients, but 12 out of 21 failed to respond.

Strict laboratory control is essential when cycloserine is used for treatment of urinary infections.

We thank our clinical colleagues for their close co-operation throughout this investigation, and Messrs. Eli Lilly and Company for the supply of cycloserine.

References

Herrold, R. D., Boand, A. V., and Kamp, M. (1955). *Antibiot. Med.*, **1**, 665.
Jones, L. R. (1956). *Analyt. Chem.*, **28**, 39.
Murdoch, J. McC., Sleigh, J. D., and Frazer, S. C. (1959). *Brit. med. J.*, **2**, 1055.
Welch, H., Putnam, L. E., and Randall, W. A. (1955). *Antibiot. Med.*, **1**, 72.

THE NEUTRALIZATION OF HEPARIN AFTER PERFUSION

A COMPARISON OF PROTAMINE AND "POLYBRENE"

BY

N. G. ROTHNIE, F.R.C.S.

AND

J. B. KINMONTH, M.S., F.R.C.S.

Surgical Professorial Unit, St. Thomas's Hospital Medical School, London

The complete neutralization of heparin is essential after perfusion for open heart surgery because residual heparin can cause or aggravate a bleeding state. The proper correction of heparin by a neutralizer can be ensured by the use of a simple test, the thrombin clotting-time of plasma, which can be made very sensitive to traces of heparin. Its method of performance and use in practice have been previously described (Rothnie and Kinmonth, 1960).

The rapid reversal of the effect of heparin and the restoration of haemostasis after operation requires an efficient heparin neutralizer. The variation and uncertainty of adequate heparin neutralization which we have found with protamine led us to an investigation of the use of the new antiheparin agent "polybrene" (hexadimethrine bromide). We report in this paper the results with this antidote in a series of experimental perfusions in the dog and in patients undergoing perfusion for the correction of varying cardiac abnormalities. These results are compared with those obtained when protamine was used as the antidote. From this investigation we have determined the most satisfactory amount of polybrene needed for complete heparin neutralization after perfusion.

Methods

In all the perfusions the Melrose rotating disk oxygenator was used. The blood samples were fixed with 3.8% (w/v) of trisodium citrate in the ratio of 9 volumes to 1. They were obtained through a small cannula in the inferior vena cava inserted through the saphenous vein in the groin (Rothnie *et al.*, 1960). Citrated platelet-poor plasma was obtained by centrifuging the blood at 3,000 r.p.m. for 5–10 minutes.

The thrombin clotting-time was obtained by adding a thrombin–calcium solution to citrated plasma and timing the clot formation. If the thrombin clotting-time was prolonged beyond the control time of 10–12 seconds, the test was repeated after adding toluidine blue to the plasma sample. If the result was more normal this was taken to indicate that the original prolongation had been due to heparin (Rothnie and Kinmonth, 1960).

The control pre-perfusion thrombin clotting-time was obtained in each case from a sample of plasma taken before heparinization, and subsequent clotting-times after perfusion were compared with this.

Heparin was given intravenously to each case immediately before caval and femoral cannulation and its antidote by the same route after removal of these cannulae, about 10–15 minutes after stopping perfusion.

Results with Protamine

In a series of 19 perfused dogs, which were given heparin 2.5 mg./kg. (donor blood 25 mg./500 ml.) and protamine as the antidote, 11 had troublesome bleeding afterwards due to residual heparin. Of these 11 bleeders, five died of continuous oozing after operation and had received protamine 2.5 or 3.75 mg./kg. (ratio of protamine to heparinizing dose of 1:1 or 1.5:1). Haemothoraces occurred in the other six bleeders and contributed to the death of two of them. These six cases were given varying doses of protamine from 2.5 to 7.5 mg/kg. (1:1 to 3:1). The remaining eight dogs in the series were non-bleeders, and most of them received protamine 7.5 or 10 mg./kg. (3:1 or 4:1).

Thus as a result of increasing the dose of protamine and ensuring that there was no residual heparin by means of the thrombin clotting-test, we were able to reduce the incidence of oozing after perfusion and eliminate the immediate mortality from this cause. There was, however, a variation in the amount of protamine necessary for the complete neutralization of heparin. In some dogs a ratio of 2:1 was sufficient and in others a ratio of 4:1 was required.

A similar variation in protamine requirements was found in six patients (average weight 30 kg.) who underwent perfusion for the correction of varying cardiac abnormalities. They received heparin 2.5 mg./kg. and doses of protamine varying from 3.75 mg./kg. (1.5:1) to 7.5 mg./kg. (3:1). After perfusion two of them had troublesome bleeding due to residual heparin and had received a total dose of protamine of 5 mg./kg. (2:1) and 7.5 mg./kg. (3:1). Details of the thrombin clotting-times in these two patients were previously reported by us in stressing the importance of the proper correction of unneutralized heparin (Rothnie and Kinmonth, 1960). One other patient, who had a trace of heparin after the administration of protamine 5 mg./kg. (2:1), had an increased post-operative drainage compared with the three non-bleeders. None of these six patients, who were perfused for an average time of 32 minutes, had any evidence of a defect of a major clotting factor. The average post-operative drainage in 24 hours was 40 ml./kg. (lowest 15 ml./kg.; highest 80 ml./kg.).

The results in these experimental and clinical cases showed that for the adequate neutralization of heparin there was a variation in the requirements of protamine from 1.5:1 to 4:1 (see Table).

Results in Experimental and Clinical Cases

Heparin Antidote	Total No. of Cases	Heparin Dose	Ratio of Antidote to Heparin	Non-Bleeders	Bleeders	
					Heparin	Other Causes
Protamine	19 dogs	2·5 mg./kg.	1:1	—	2	—
			1·5:1	—	5	—
			2:1	1	—	—
			2·5:1	1	2	—
			3:1	3	1	—
			4:1	3	1	—
	6 patients	2·5 mg./kg.	1·5:1	2	1	—
			2:1	1	1	—
			3:1	—	1	—
	25 cases			11	14	—
Polybrene	30 dogs	2 mg./kg.	1:1	10	—	3 surgical
			1·5:1	16	—	1 surgical
	7 patients		1·5:1	7	—	—
	18 dogs	2·5 mg./kg.	1·5:1	17	—	1 low fibrinogen
	5 patients		1·5:1	5	—	—
	60 cases			55	—	5

Results with Polybrene

In this investigation polybrene was used in a series of 48 experimental perfusions in the dog and in 12 patients perfused for the open correction of varying cardiac defects.

Experimental Series

In 30 of these perfusions the dogs were given heparin 2 mg./kg. and the donor blood 20 mg./500 ml., and were perfused for a mean time of 37 minutes. The remaining 18 dogs received heparin 2.5 mg./kg. and the donor blood 25 mg./500 ml., and were perfused for an average of 49 minutes. These doses of heparin gave satisfactory anticoagulation and protection of the clotting elements during perfusion.

In all these dogs thrombin clotting-times were assessed on plasma samples taken before heparinization, after perfusion and 5–10 minutes after the administration of polybrene. In 22 dogs, plasma samples were tested at intervals up to two hours after perfusion.

Of the 30 dogs given heparin 2 mg./kg., 19 received an initial dose of polybrene of 2 mg./kg. (ratio 1:1), and 11 a dose of 3 mg./kg. (ratio 1.5:1). Four of the 19 dogs were found to have a trace of heparin as shown by the thrombin-clotting test 5–10 minutes after giving the antidote. They required a further 1 mg. of polybrene per kg., making a total of 2 mg./kg. (1.5:1), for complete neutralization. The remainder (15) of the 19 dogs showed adequate heparin neutralization, but subsequently two of them received a small transfusion (200–400 ml.) of heparinized blood from the heart–lung machine, which necessitated giving more polybrene to a total of 3 mg./kg. (1.5:1). Each of the 11 dogs receiving one dose of polybrene of 3 mg./kg. (1.5:1) showed satisfactory neutralization of heparin.

Thus in 30 experimental perfusions, heparin was completely neutralized by polybrene in a dose of 2 mg./kg. in 13 dogs and of 3 mg./kg. in 17 dogs. The most satisfactory neutralizing dose of polybrene for a heparinizing dose of 2 mg./kg. (see Table) was therefore 3 mg./kg. or a ratio of polybrene to heparin of 1.5:1.

The 18 dogs who received heparin 2.5 mg./kg. were given this ratio of polybrene—that is, a dose of 3.75 mg./kg.—and each was found to have adequate neutralization of heparin.

In 22 of the 30 perfusions (heparin 2 mg./kg.) which showed adequate heparin neutralization 5–10 minutes after giving the antidote further thrombin clotting-times were assessed on plasma samples taken 30, 60, and 120 minutes afterwards. Ten of these dogs were given polybrene 2 mg./kg. (1:1) and 12 3 mg./kg. (1.5:1). The thrombin clotting-times of each dog up to two hours after administering the antidote were similar to that of the pre-perfusion plasma control. The neutralization of heparin was therefore complete within 10 minutes of giving these doses of polybrene and was satisfactorily maintained. No anticoagulant was found to appear subsequent to adequate neutralization.

In each of the 48 experimental perfusions satisfactory heparin neutralization was achieved with polybrene and there was no instance of bleeding due to residual heparin. In the first 30 dogs there were four cases of abnormal bleeding. They were due to surgical causes and no evidence of a clotting defect was found. In the remaining 18 dogs there was one bleeder. This was due to a much-reduced fibrinogen concentration (ca. 10 mg./100 ml.) after a perfusion lasting one hour in a dog which, before operation, had a low fibrinogen concentration of 100 mg./100 ml. The donor blood was also poor in fibrinogen (180 mg./100 ml.).

Complete neutralization was best achieved by giving 1.5 mg. of polybrene for every milligram of the heparinizing dose given to the case—that is, a ratio of 1.5:1.

Clinical Series

This series consisted of 12 patients, seven of whom were given heparin 2 mg./kg. (donor blood 20 mg./500 ml.), and five heparin 2.5 mg./kg. (donor blood 25 mg./500 ml). Each received 1.5 mg. of polybrene for each milligram of heparin given to the patient (ratio 1.5:1). The duration of perfusion varied from 20 minutes to over two hours.

By means of the thrombin clotting-time complete heparin neutralization was found in each patient 10 minutes after giving this dosage ratio of polybrene, and there was no instance of bleeding due to unneutralized heparin. The average post-operative drainage for 24 hours in six patients (average weight 28.7 kg.), who were comparable to the six patients described above and given protamine, was about 21 ml./kg. in 24 hours (range of 10–40 ml./kg.). This compares with an average of 40 ml./kg. for the patients given protamine which was quoted above.

In five patients in this series thrombing clotting-times were estimated on plasma samples taken 5–10, 30, and 90 minutes after administration of the polybrene. In each patient the clotting-times at these intervals were similar to the pre-perfusion control time, and there was no evidence of the reappearance of heparin (Fig. 1).

In one patient receiving heparin 2 mg./kg., a dose of polybrene 2 mg./kg. (1:1) was given initially. Tests after this showed adequate neutralization (Fig. 2). A small transfusion of 200 ml. of heparinized blood was then given. The thrombin clotting-time after this was increased owing to the presence of heparin, the concentration of which would have been enough to delay coagulation. A further 1 mg. of polybrene per kg. (total dose 3 mg./kg.—that is, 1.5:1) neutralized the residual heparin.

This case further emphasizes the experimental finding that polybrene in a ratio of 1:1 may be only just sufficient for adequate neutralization and provides little reserve to cover the variations in the total circulating heparin that might occur owing to perfusion.

As in the experimental perfusions, polybrene in a dose of 1.5 mg. for each milligram of the heparinizing dose to the patient was found to be consistent and satisfactory. We did not find any evidence that this amount of polybrene produced any adverse effect on the clotting mechanism.

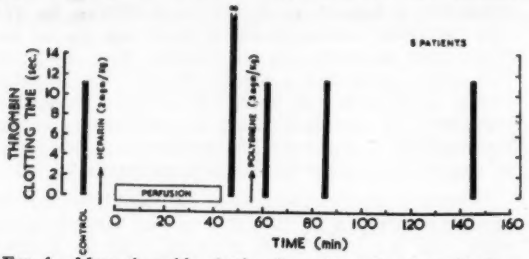


FIG. 1.—Mean thrombin clotting-times charted at intervals from the start of perfusion in five patients. Indicates incoagulable plasma.

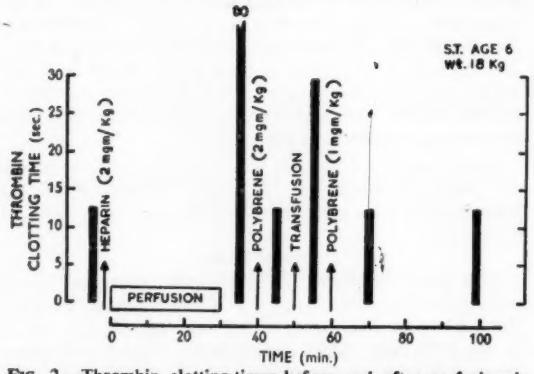


FIG. 2.—Thrombin clotting-times before and after perfusion in a patient initially given polybrene 2 mg./kg. and requiring a further 1 mg./kg. after a transfusion of heparinized blood (200 ml.). ∞ Indicates incoagulable plasma.

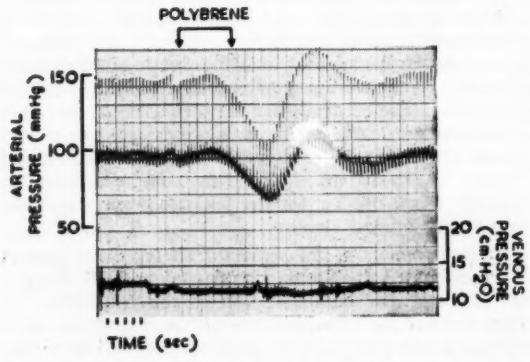


FIG. 3.—Arterial and venous pressure tracing to show the effects of rapid injection of polybrene (6 seconds) intravenously.

Reaction to Polybrene Injection.—When given rapidly to the perfused dog in about 5 seconds there was a transient drop in arterial pressure, which rapidly returned to normal in about 15 seconds, with no change in venous pressure (Fig. 3). The rapid injection of an equal volume of normal saline under similar conditions produced no such change in arterial pressure, showing that the reaction was most likely due to the polybrene itself. This hypotensive effect of polybrene appears to be less marked and less prolonged than that found by Hurt *et al.* (1956) after the rapid injection of protamine in perfused dogs.

When polybrene was given undiluted and slowly in two to three minutes, no change in arterial or venous pressure was noted in the perfused dog or patient.

Discussion and Conclusions

The heparin present in the patient after perfusion is derived from two main sources. One is the heparinizing dose given to the patient and the other the perfused heparinized donor blood. In each perfusion the first is a constant amount based on the body weight of the patient; the second is a variable amount depending on how much donor blood is used. When these two sources are mixed during bypass the result is usually a variable increase in the amount of heparin requiring neutralization in the patient at the end of perfusion.

To neutralize this variable amount of heparin it is thus not entirely accurate to base the antidote requirements on the heparinizing dose of the patient. It is, however, convenient to relate the dose of antidote to it, and hence to body weight, provided an allowance is made for the increased heparin. It is usually expressed as a ratio of milligrams of antidote for each milligram of heparin given to the patient.

In practice, we have therefore given at the end of perfusion such a dose of antiheparin agent based on body weight. The presence of any unneutralized heparin after this was detected or excluded by the thrombin clotting-time and further antidote given if necessary. In this way we have determined the most satisfactory dose of antidote necessary for complete heparinization after perfusion.

Although adequate heparin neutralization could be achieved in our series with protamine, this agent was not entirely satisfactory because of its inconsistent and variable neutralizing activity. This could be partly due to the varying amount of heparin present after perfusion, but there was no evidence that such heparin variations predominated in the cases given protamine. The variable activity is more likely to be due to the varying potency of the preparations of this biological product and to competition for the agent, unlike polybrene, between the plasma proteins, especially fibrinogen, and heparin.

We have not encountered hypotensive reactions (Hurt *et al.*, 1956), provided the protamine is given slowly, nor have we observed any anticoagulant effect (Andersen *et al.*, 1959) with the doses we have used in the cases reported above. Neither of these side-effects of protamine appears to us to contraindicate its use after perfusion. However, dissatisfaction with its efficiency as a heparin neutralizer led us to investigate the suitability of other antiheparin agents.

Toluidine blue has been used clinically but is slow and uncertain in its action, with side-effects which preclude its use after perfusion (Allen *et al.*, 1949; Bickers, 1953; Weiss *et al.*, 1958). The more recently introduced antiheparin agent is polybrene (Preston and Parker, 1953). It is a basic polymer of a quaternary ammonium salt with the generic name hexadimethrine bromide.

A dose of 1 mg. of polybrene for each milligram of the heparinizing dose given to the patient (ratio of 1 : 1) is the amount recommended by Weiss *et al.* (1958) and by Keats *et al.* (1959) after perfusion. These workers used the whole-blood clotting-time to detect adequate

heparin neutralization. We have previously pointed out that this clotting-test is a poor indicator of heparin activity (Rothnie and Kinmonth, 1960). With the use of the more sensitive thrombin clotting-time some of our experimental cases showed incomplete neutralization of heparin with this 1:1 ratio of the antidote. Evidence was found in other cases that such a dose was only just enough to complete neutralization. This slight variation in polybrene requirements is most likely due to the variable amount of heparin present after perfusion. Since it is important to neutralize the anticoagulant completely, we have used a polybrene-to-heparin ratio of 1.5:1, and this has consistently been satisfactory.

With this dose of polybrene we have noted no inhibitory effects of the drug on coagulation. The problem of the anticoagulant effect of polybrene, and of protamine (Andersen *et al.*, 1960), has been investigated and will be the subject of another report. There appears to be a wide margin of safety with both agents and no danger of inhibiting coagulation with the doses used clinically.

Neutralization by polybrene, as with protamine, is prompt, and once the heparin has been completely neutralized we have found no evidence of the reappearance of the anticoagulant in the circulation. This theoretical reappearance must not be confused with the term "heparin rebound" which has been given to a period of hypercoagulability of the blood after prolonged heparin administration (Cate *et al.*, 1954).

If a transfusion of heparinized blood is given to the patient after perfusion, we have found it advisable to cover this extra heparin with polybrene. A dose of 1 mg. of polybrene for each milligram of heparin in the transfused donor blood is a convenient and adequate amount.

The slow administration of polybrene produced no hypotensive effects, but careful observation of the arterial pressure should be made during the injection, which should be temporarily stopped if the pressure falls.

Although our comparison of the amount of postoperative drainage after each antidote involved only a small number of patients, our findings that polybrene was superior to protamine are in agreement with those of a larger comparative series studied by Lillehei *et al.* (1960).

This investigation has shown that polybrene, when compared with protamine, is more consistent as a heparin neutralizer after perfusion and more effective in eliminating residual heparin as a cause of abnormal bleeding.

Summary

An investigation of the neutralization of heparin by protamine and "polybrene" (hexadimethrine bromide) after perfusion of experimental and clinical cases has been made, using the thrombin clotting-time as the indicator of heparin activity.

Protamine was found to be variable and uncertain in its neutralizing activity and the reasons are briefly discussed. Polybrene was the more consistent and effective antiheparin agent, and a dose of 1.5 mg. for each milligram of the heparinizing dose given to the patient was found to be satisfactory.

The hypotensive and anticoagulant side-effects of these agents were not noted with the doses and method of administration recommended.

We are indebted to Miss Sheila Maughan and Miss Diana Hulkes for skilled technical assistance, to Dr. G. I. C. Ingram for much helpful advice, and to other members of our surgical perfusion team for their help in the work. The polybrene was kindly supplied by Abbott Laboratories Ltd.

REFERENCES

Allen, J. G., Grossman, B. J., Elghammer, R. M., Moulder, P. V., McKeen, C. L., Jacobson, L. O., Pierce, M., Smith, T. R., and Crosbie, J. M. (1949). *J. Amer. med. Ass.*, **139**, 1251.
Andersen, M. N., Mendelow, M., and Alfano, G. A. (1959). *Surgery*, **46**, 1060.
—— —— —— (1960). *J. thorac. Surg.*, **39**, 613.
Bickers, W. (1953). *Amer. J. Obstet. Gynec.*, **66**, 1313.
Cate, W. R., Sadler, R. N., Seitzman, D. M., and Light, R. A. (1954). *Amer. Surg.*, **20**, 813.
Hurt, R., Perkins, H. A., Osborn, J. J., and Gerbode, F. (1956). *J. thorac. Surg.*, **32**, 612.
Keats, A. S., Cooley, D. A., and Telford, J. (1959). Ibid., **38**, 362.
Lillehei, C. W., Sterns, L. P., Long, D. M., and Lepley, D. (1960). *Ann. Surg.*, **151**, 11.
Preston, F. W., and Parker, R. P. (1953). *A.M.A. Arch. Surg.*, **66**, 545.
Rothnie, N. G., and Kinmonth, J. B. (1960). *Brit. med. J.*, **1**, 73.
—— Norman, A. G., Steele, M., and Kinmonth, J. B. (1960). *Brit. J. Surg.* In press.
Weiss, W. A., Gilman, J. S., Catenacci, A. J., and Osterberg, A. E. (1958). *J. Amer. med. Ass.*, **166**, 603.

TRANSVENTRICULAR MITRAL VALVOTOMY DURING PREGNANCY

BY

J. M. REID, M.D., M.R.C.P.Ed.
Senior Registrar

R. L. BERGER,* M.D.
Registrar

AND

J. G. STEVENSON, M.D., F.R.F.P.S.
Consultant Physician

Department of Thoracic Surgery, Mearnskirk Hospital, Renfrewshire

The surgical relief of rheumatic mitral stenosis now meets with universal acceptance. In pregnancy the mechanical impediment of the narrowed valve is further aggravated by the physiological alterations in the circulation, particularly during the second trimester. The place of mitral valvotomy during pregnancy is still under discussion, and references to the operation in such circumstances in the world literature are still sparse. The earliest reports were by Brock (1952), Cooley and Chapman (1952), and Logan and Turner (1952). These three papers described a total of seven cases of valvotomy during pregnancy. Since then the total has risen to 133. All these operations were performed by the finger method or by a suitable knife via the atrium.

Present Series

The purpose of this communication is to add a description and an analysis of a further 10 patients operated on during pregnancy by the transventricular route assisted by a mechanical splitter, first used and described by Logan and Turner (1959).

The Table summarizes the salient features of the 10 patients in this series.

*Now Chief Resident (3rd Surgical Service and Laboratories), Boston City Hospital.

Seven patients were at the stage of pregnancy when the physiological burdens were either developing or at their maximum. It is relevant to note here that in all these patients deterioration in their grading occurred progressively. This is in accord with the general experience. Five had weathered pregnancy on previous occasions. In four instances they had shown evidence of congestive failure at that time and all had been coped with by orthodox medical measures with rest in bed, diuretics, etc.

Pulmonary congestion was uniformly present in all our cases, and some had pleural effusions. Atrial fibrillation was the rhythm pre-operatively in Case 3, and it persisted afterwards. At operation tight mitral stenosis was confirmed on each occasion. One patient (Case 10) died 18 hours after operation. Fuller consideration is given to this fatal outcome below. Four patients developed transient atrial fibrillation. In one instance pulmonary congestion increased post-operatively, but responded to diuretic therapy. Another patient developed thrombophlebitis, which subsided uneventfully. Otherwise the operation was tolerated as satisfactorily in these patients as in the non-gravid state.

The immediate result in the first nine patients was excellent. Of the nine, four who were totally incapacitated and two who were moderately so were enabled, after operation, to become ambulant and to pursue limited activities in their own homes during the remainder of their pregnancy. The other three, all of whom were in the early weeks of pregnancy and were not seriously incapacitated, had a normal mitral valvotomy and continued their pregnancy actively and successfully. Premature labour occurred in Cases 6 and 10, and in the former the foetus was macerated.

The follow-up of our patients has varied from one to three years. Their functional gradings in May, 1960, compare favourably with their pre-operative status, and are shown in the Table. One patient (Case 2) has undergone a further pregnancy without any cardiac disability. One other patient (Case 4) was at the time of writing five months pregnant, and, although slightly breathless, was coping adequately with her normal household duties.

Discussion

During pregnancy the blood volume begins to increase in the second trimester to reach a peak early in the third, after which it gradually falls, only to rise again during labour and immediately afterwards. The augmentation of blood volume to its highest level (50% above normal) at the 32nd week is accompanied by a corresponding rise in cardiac output, heart rate, and oxygen consumption. These alterations in circulatory dynamics are well tolerated by the normal heart, but in patients with mitral stenosis such a haemodynamic burden seriously embarrasses the heart, and may well precipitate severe cardiac failure with acute pulmonary oedema. The effect of this progressive load on the circulation is well illustrated by the steady increase of symptoms shown by seven of our patients. In functional grading they all increased at least two grades in severity, and five developed intractable cardiac failure only partially held by orthodox medical treatment.

Prior to the introduction of operation during pregnancy, the corner-stone of treatment was protracted bed rest. Under the influence of medical measures pregnancy could be continued in the lower grades of functional disability with comparative safety to the mother. Friedberg (1956) quoted a maternal mortality of 2% in grades 0–II. However, in the more severe grades, III and IV, there is a drastic increase in maternal mortality to 40% (16 deaths in 40 patients). That author found it difficult to foretell when serious failure might occur in individual cases. Mendelson (1955) arraigned cardiac disease as to-day's single greatest cause of maternal mortality. Hamilton (1947) reviewed 1,335 cases of heart disease in pregnancy, of which 93% were rheumatic. The foetal mortality in this series was 8.6% in the favourable group and 31% in the unfavourable group. In essence medical treatment can offer in favourable cases a high survival rate for both mother and child, but with severe restrictions on the mother's activity for the duration of pregnancy. In unfavourable cases the alarmingly high maternal and foetal death rate warrants a more active policy in the way of surgical intervention.

Although up to the present comparatively few reports of valvotomy during pregnancy have been published,

Summary of Cases

Case No.	Age	Pregnancy	C.C.F. in Previous Pregnancies	Grading at Start of Pregnancy and Pre-operatively	Duration of Pregnancy (Weeks)	X-ray Appearances	Date of Operation	Fate of Foetus	Method of Delivery	Grade in May, 1960	Subsequent Pregnancies
1	23	3rd	During 2nd	I–III	18	No pulmonary congestion	26/6/57	Alive and well	Normal P.V.	I	Nil
2	22	1st	Nil	I–I	6	,, ,, ,,	1/7/57	,, ,,	,, ,,	0	One—alive and well
3	27	1st	,,	I–IV	20	Severe pulmonary congestion with bilateral effusions	9/8/57	,, ,,	P.V. (forceps)	I	Nil
4	28	1st	,,	0–II	8	No pulmonary congestion	2/12/57	,, ,,	Normal P.V.	I	5 months pregnant now
5	26	2nd	During 1st	I–I	8	No pulmonary congestion. Kerley's lines present	24/2/58	,, ,,	,, ,,	0	Nil
6	34	2nd	,, ,,	I–III	29	Pulmonary congestion present	26/2/58	Macerated. Stillborn (13/3/58)	,, ,,	I	,,
7	21	1st	Nil	0–IV	20	Marked pulmonary congestion	30/4/58	Alive and well	,, ,,	0	,,
8	26	2nd	During 1st	I–IV	28	,, ,,	17/4/59	,, ,,	Caesarean section + sterilization	I	,,
9	24	3rd	,, 2nd	I–IV	22	,, ,,	17/8/59	Twins, alive and well	Normal P.V.	0	,,
10	22	1st	Nil	II–IV	20	Severe pulmonary congestion with bilateral effusions	4/12/59 (died 18 hours later)	Died			

and experience must therefore be necessarily limited, certain inescapable facts have come to light. Among the total of 133 cases so far accumulated there have been five maternal and nine foetal deaths. The majority of these patients fell into the unfavourable group (grades III and IV), and in most of them surgery was tolerated as well as in the non-pregnant state. They were able to continue the remainder of their pregnancy without undue limitation on their activities. In addition, Watt, Bigelow, and Greenwood (1959) followed up their series of 24 patients operated on during pregnancy, with neither maternal nor foetal mortality, for one to six years. They found that all had reverted to either grade I or II from a pre-operative grading of III or IV.

Our 10 patients were operated on by the transventricular route, using a mechanical dilator, the method we have employed exclusively since late 1956. In our unit 250 valvotomies have been performed with this instrument, and the uniformly satisfactory commissurotomy compares, we feel, very favourably with the uncertainty of the digital methods. The previous operations described in pregnancy appear to have been carried out through the atrium by the combination of finger and knife. In the series of 37 cases reported by Dogliotti *et al.* (1960) no mention is made of the actual technique, but as his cases date from 1953 the implication is that a conventional digital method has been used. Our experience is that instrumental valvotomy is tolerated equally well in the pregnant and non-pregnant state. In addition, we believe that the more certain relief of mitral obstruction obtained by the instrument is of double importance in the overburdened circulation of a pregnant woman suffering from mitral stenosis.

One of our patients (Case 10) died 18 hours postoperatively. At the beginning of pregnancy she was in grade II, but she progressed steadily to grade IV by the twentieth week. By this stage she was orthopnoeic, showed marked pulmonary congestion, and had bilateral pleural effusions. Operation was urgent if the mother's life was to be saved. During anaesthetic induction, cyanosis and peripheral circulatory collapse became rapidly obvious. Thoracotomy, promptly performed, revealed the heart in asystole. Expeditious valvotomy was carried out, and after cardiac massage for several minutes cardiac contractions returned, though the output was manifestly ineffective. She failed to regain consciousness and died next morning. Surgery at an earlier stage of this woman's pregnancy or prior to pregnancy might well have saved her life.

From the accumulated accounts of the surgical treatment of mitral stenosis in pregnancy and in the light of our own experience, we believe that operation is a safe and valuable procedure in those patients. In the absence of a reliable guide to the stability of functional grading in pregnant women with mitral stenosis, it seems reasonable to advocate operation if serial assessments indicate progressive cardiac disability. In grades III and IV the case for operation is even stronger. From the point of view of maternal safety, operation in the early months of pregnancy would avoid entirely the necessity for urgent intervention in the face of grave circulatory embarrassment.

Summary and Conclusions

The relevant literature on mitral valvotomy during pregnancy is briefly reviewed and a further 10 cases are described.

All patients were subjected to a transventricular operation, with very satisfactory short- and long-term results in all but one instance. A plea is made for the serious consideration of operative intervention in those patients, in view of their established tendencies to deteriorate clinically during the course of pregnancy.

We thank Mr. R. S. Barclay for his help and encouragement in the preparation of this paper and for his permission to have it published. We also thank the physicians and obstetricians who referred their patients for surgical treatment.

References

Brock, R. C. (1952). *Proc. roy. Soc. Med.*, **45**, 538.
Cooley, D. A., and Chapman, D. W. (1952). *J. Amer. med. Ass.*, **150**, 1113.
Dogliotti, A. M., Dellepiane, G., Dato, A. A., Gentilli, R., and Siliquini, P. N. (1960). *J. thorac. Surg.*, **39**, 5, 663.
Friedberg, C. K. (1956). *Diseases of the Heart*, 2nd ed., p. 1093. Saunders, Philadelphia.
Hamilton, B. E. (1947). *Amer. Heart J.*, **33**, 663.
Logan, A., and Turner, R. (1952). *Lancet*, **1**, 1286.
—— —— (1959). Ibid., **2**, 874.
Mendelson, C. L. (1955). *Amer. J. Obstet. Gynec.*, **69**, 1233.
Watt, G. L., Bigelow, W. G., and Greenwood, W. F. (1959). Ibid., **77**, 507.

TREATMENT OF SEVERE HYPERTENSION WITH BRETYLIUM TOSYLATE

BY

E. F. D. MONTUSCHI, M.D., M.R.C.P.

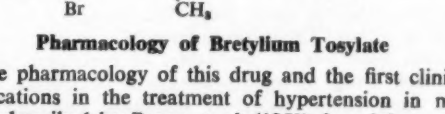
H. E. S. PEARSON, M.D., M.R.C.P.

AND

L. L. WILSON,* M.B., B.S., M.R.C.P.Ed.

The Whittington Hospital, London

Bretylium tosylate ("darenthin") is N-*o*-bromobenzyl-N-ethyl-N:N-dimethylammonium *p*-toluenesulphonate.



Pharmacology of Bretylium Tosylate

The pharmacology of this drug and the first clinical applications in the treatment of hypertension in man were described by Boura *et al.* (1959), in a joint paper from the Wellcome Foundation and University College, ten years after Arnold and Rosenheim (1949) first reported the use of the salts of hexamethonium in the treatment of hypertensive disease. A benzyl quaternary ammonium compound, it has no evident anticholinergic action, but selectively blocks the peripheral sympathetic (adrenergic) nerves, where its preferential accumulation has been demonstrated by radioactive techniques. Its action therefore differs in an important way from that of the earlier ganglioplegic agents, in which the concomitant parasympathetic block is a clinical disadvantage, and also from that of the secondary and tertiary amines, mecamylamine and pempidine, which enter the body cells and may, in addition, cause side-effects by their central action (Bennett *et al.*, 1957).

Adrenergic nerve blockade is not, it should be recalled, the same as adrenalytic effect. On the contrary, just as denervated vessels become hypersensitive to the action of circulating adrenaline and noradrenaline, so

*Present address: c/o Cleveland Clinic, Cleveland 6, Ohio.

the vasoconstrictor effects of these substances and their action on the nictitating membrane of the cat are increased after administration of bretylium tosylate. A very severe hypertensive crisis was observed in a patient with a phaeochromocytoma after intravenous administration of bretylium (Boura *et al.*, 1959). This, however, is not a constant effect, as it did not occur in another similar case (Rosenheim, personal communication).

The chemical sympathectomy thus achieved by bretylium tosylate causes orthostatic hypotension in the experimental animal and in man, more conspicuously in the hypertensive subject, by release of vasoconstrictor tone, and the isolated nature of its action offers the clinician "a hypotensive agent of a new type" (Boura *et al.*, 1959).

The purpose of this paper is to describe our experiences with bretylium tosylate in the treatment of 75 cases of severe hypertension over a period of nine months. Of these, 65 have received the drug for more than six months continuously.

Method

Bretylium tosylate was used throughout by the oral route in tablets containing 200 mg. of the salt (112 mg. of the base). The tablets are scored in half so that doses of 100 mg. are given easily. The drug has been administered at approximately eight-hour intervals and always before meals, as this facilitates absorption. Every patient who had not previously been treated with ganglion-blocking agents was admitted to hospital for preliminary investigation and for the initial stages of treatment. The investigations were directed to assess the possible cause and severity of the hypertension, with special regard to cardiac and renal function. The fundal appearances were carefully noted.

A number of patients who had been treated over a period of time with mecamylamine and pempidine, whether or not in combination with reserpine, hydrallazine, and oral diuretics, and who had been followed up at regular intervals at the hypertensive clinic, were switched, either gradually or suddenly, from the ganglion-blocking agent they were taking to bretylium tosylate without admission to hospital. At first the dose relation used was of one tablet of bretylium tosylate for each 5 mg. of mecamylamine or pempidine, but it was soon found wiser to substitute one tablet of bretylium tosylate for each 10 mg. of the other drugs.

In order to assess the action of bretylium tosylate, no other hypotensive agent was given in the initial stages of treatment to any patient. Later, the oral diuretic, hydroflumethiazide, was added in a number of cases. In previously untreated cases the initial dose of bretylium tosylate was 100 mg. eight-hourly, as it was soon found that even this small dose could give rise to marked postural hypotension. The dose was increased by 100 mg. t.i.d. every other day and in demonstrably less responsive cases by 200 mg. t.i.d. until the desired effect was obtained. While in hospital, blood-pressures were recorded in the lying and standing positions four hours after each dose and more frequently when required. In out-patients blood-pressures were also recorded in both postures and approximately four hours after the last dose of the drug. Fundal appearances were noted at monthly intervals, and the urine, blood urea, and, where necessary, the serum electrolytes, were periodically determined.

Classification of Cases

Table I shows the grouping of cases in our series.

By severe benign hypertension (group A) we mean uncomplicated hypertension with diastolic pressures of 120+ mm. Hg at rest.

TABLE I.—*Grouping of Cases*

Group	No. of Cases	Male	Female	Average Age in Years	No. of Cases Previously Treated with Ganglion-blocking Agents
A. Severe benign hypertension	7	6	1	49	4
B. Severe benign hypertension with cardiac involvement	39	19	20	50	18
C. Severe benign hypertension and blood urea greater than 50 mg./100 ml.	13	7	6	55	6
D. Malignant hypertension	13	6	7	53	7
E. Severe benign hypertension in pregnancy	3	0	3	30	0
Total	75	38	37	48	35

Group B (severe benign hypertension with cardiac involvement) comprises patients with hypertensive heart failure, both incipient and established, patients with associated coronary disease, and a few cases which, although symptomless, were found to have marked cardiac enlargement and T-wave inversion in the left ventricular surface leads of the electro-cardiogram.

Group C comprises all patients found to have albuminuria and renal failure (blood urea more than 50 mg./100 ml.) in the absence of congestive cardiac failure; aetiologically they are a heterogeneous group, as it was not always possible to establish with certainty whether renal failure was due to chronic glomerulonephritis, to chronic pyelonephritis, or to renal ischaemia which followed essential hypertension. This group does not include toxaemia of pregnancy and malignant hypertension.

Group D comprises all patients with severe diastolic hypertension and papilloedema irrespective of the aetiology of the hypertensive state and of the complications ensuing. They have been grouped separately because they are the obvious measuring-rod for assessing the results of hypotensive treatment (Harington *et al.*, 1959).

Group E (benign hypertension in pregnancy). Only three patients were thought to be suitable for treatment with bretylium tosylate. When toxaemia of pregnancy coexists or is the cause of the hypertensive state, bedrest is imperative, and bretylium tosylate was found to be an ineffective hypotensive in the supine position.

Results

The results of treatment in the various case groups are shown schematically in Table II. In general, a response was classified as satisfactory when, without interference with the patient's usual habits of work and leisure, the orthostatic diastolic blood-pressure could be maintained at about 90 mm. Hg. In the most severe and the malignant cases higher average diastolic pressures were accepted as satisfactory if they were accompanied by evidence or regression of the ocular and electrocardiographic signs and by a falling level of the blood urea.

Table II.—*Response to Treatment in 75 Cases*

Group:	A	B	C	D	E	Total
Satisfactory with a low dosage of bretylium tosylate. Less than 1,000 mg. a day ..	2	9	2	0	1	14
Satisfactory with a high dosage of bretylium tosylate. More than 1,000 mg. a day ..	3	20	9	7	0	39
Intolerance of optimum dosage	0	2	1	3	0	6
Poor response	0	0	1	2	2	5
Discontinued because of side-effects or some other contra-indication	2	8	0	1	0	11

The minimal effective dose for prolonged administration has varied from 100 to 1,800 mg. t.i.d. With a single exception, it has been found that some increase in dosage is necessary in order to maintain control after the patient has left hospital, and there has not infrequently been some anxiety about whether the ultimate effective dose will exceed the patient's capacity. Our upper limit of 1,800 mg. t.i.d. is low by some standards, but we have found that to give large numbers of the same tablets impairs the patient's confidence in the efficacy of the treatment, upsets his digestion, and makes him feel that his condition must be very serious. We have taken a total daily dose of 1 g. as an arbitrary level above which this difficulty may be encountered in some degree. We have found, as explained below, that the adjuvant effect of hydroflumethiazide has been most helpful in limiting the numbers of patients in whom the optium dose cannot be attained.

Satisfactory control of blood-pressure in the orthostatic position does not, of course, necessarily mean satisfactory control of the disease process. Two of our patients have died, one of rapidly progressive cardio-renal failure and one of a cerebral haemorrhage. Another four, two with malignant hypertension and all with renal impairment at the onset of treatment, are deteriorating, and a second patient has had a massive cerebral haemorrhage evacuated surgically. In two cases the dose cannot be adequately raised, because profound orthostatic hypotension aggravates a pre-existing cerebral ischaemia and we have had to be content with more modest control over the blood-pressure. These are incidents and hazards which are always met in the treatment of any series of patients with severe hypertensive disease.

An unsatisfactory response was obtained in 2 of the 13 patients with malignant hypertension and in a third patient in whom polyarteritis nodosa is suspected. The other two failures were in pregnant women and were attributed to recumbency.

The drug has had to be discontinued in nine cases because of side-effects or the development of cardiac or cerebral complications. One patient returned to her previously well-established treatment with pentolinium and another to reserpine alone, with moderate control. Three patients have changed to trimethidinium and one to guanethidine. So far no patient has been reverted to mecamylamine or pempidine, although we still have a number who remain satisfactorily controlled with these drugs.

Side-effects

Postural Hypotension

Although the establishment of postural hypotension is the aim of treatment with this drug, a reduction of blood-pressure that is so sudden and profound as to cause a disabling cerebral anoxia must be regarded as an unwanted side-effect.

It was met with more frequently at the onset of treatment; and one patient, a woman of 40 with malignant hypertension, showed at first a "spirit-level" type of response to a single dose of 100 mg., but now requires 1,200 mg. t.i.d. with added hydroflumethiazide. In other cases the difficulty has persisted until the treatment has had to be abandoned. We agree with Turner and Lowther (1960) that giddiness is a difficult symptom to evaluate, as it is not necessarily linked with the severity of the hypotension. It appears that the individual response to the sudden fall in blood-pressure varies as widely as does the response to the fall in blood volume in the "dumping syndrome" as described by Le Quesne *et al.* (1960).

Some patients have particularly complained of giddiness or faintness on getting up at night to empty the bladder, causing a fall on one occasion, and there have also been several complaints of the same symptoms after exertion, such as climbing stairs, as Lowe and Rosenheim (1960) have observed.

In five cases pain in the nape has occurred at the height of the hypotensive effect, especially if the patient exercises at this time (Montuschi, 1957). In three of these patients the symptom, which had been noticed while they were previously under treatment with parenteral pentolinium, disappeared when change was made to mecamylamine and reappeared when bretylium tosylate was substituted for mecamylamine, presumably because of the sharper orthostatic hypotensive reaction induced by this drug.

General Tiredness

This side-effect is very common and is not simply linked with fall in blood-pressure, as it persists in the sitting posture and has been noticeable in patients who had been previously treated with ganglion-blocking drugs. Tiredness is both mental and physical, and on occasion patients have reported extreme fatigue in lifting the arms to shave or to do their hair. Neuromuscular block has been reported in experimental work (Boura and Green, 1959), but only with doses of the order of 30 times those required to reduce sympathetic tone. Extreme muscle fatigue led two patients to discontinue the treatment. The electromyogram showed a myopathic pattern in one case, and a similar finding has been reported to us by Evanson (personal communication.

Stuffiness of Nose

Stuffiness of the nose and puffiness of the eyes are in our experience uncommon side-effects. They are not usually troublesome. In one case, however, a dose of 1,800 mg. t.i.d., required in order to achieve satisfactory control over the blood-pressure, provoked an intolerable rhinorrhoea with lacrimation. The difficulty was overcome by reducing the dose of bretylium tosylate to 1,200 mg. t.i.d. and adding hydroflumethiazide. With this combination of drugs the blood-pressure was adequately controlled, and only moderate nasal congestion persisted.

Parotid Pain

Sharp transient pain in the parotid region at the very onset of mastication, relieved by continued eating, is a very common side-effect. Its incidence—not less than 25%—is difficult to estimate, as it is in great part a function of duration of treatment. It rarely occurs during the first month of treatment, and more commonly becomes manifest after three to six months. This may be the reason why only four cases were

reported in the Hammersmith series. Although alarming for some patients, it is mentioned by others only on direct questioning. In one case, not of this series (Caplan, personal communication), the severity of parotid pain led to discontinuation of treatment. It is noteworthy that pain continued for a whole week after treatment was withdrawn and long after any hypotensive effect of the drug was recorded. In one of our cases the symptom persisted for three months after cessation of treatment for other reasons. This, together with the delay in onset of the symptoms, strongly suggests a slow local preferential accumulation of the drug.

The mechanism of action of this side-effect is not known, but the symptomatology suggests a spasm of the orifice of the parotid duct with transient obstruction to salivary flow. One patient experienced pain simply at the sight of appetizing food.

Gastro-intestinal Intolerance

As the drug is administered on an empty stomach, nausea and vomiting may be troublesome at high dosage. The difficulty is often circumvented by diminishing the dose of bretylium tosylate and adding an oral diuretic of the benzothiadiazine series. When the dose of bretylium tosylate is raised rapidly diarrhoea may ensue, but this quickly passes on reducing the dose and building it up again more slowly. Transient looseness of the bowels is often met with—presumably as a release phenomenon—when patients are switched from ganglion-blocking agents to bretylium tosylate.

Disorders of Micturition

Frequency of micturition and a poor stream occur not uncommonly, but have never been very troublesome and have only been noticed at high dosage.

Failure of Ejaculation

Although systematic inquiries have not been made, two patients complained of failure of ejaculation, erection being normal. Married men who had been troubled by impotence during treatment with mecamylamine (with consequent periodic lapses from treatment) have spontaneously reported satisfactory conjugal relations when treated with bretylium tosylate.

Headache

One man experienced extremely violent headaches after a single dose of bretylium tosylate, and these occurred at two successive attempts to restart treatment. There was no evidence of phaeochromocytoma and the patient is now well controlled by guanethidine. Another patient experienced throbbing headaches and palpitations—such as are more frequently met with under the action of hydrallazine—in the first two months of treatment with bretylium tosylate, but the side-effects were not severe and are becoming gradually less troublesome. They are persumably due to vasodilatation.

Shortness of Breath

Turner and Lowther (1960) mentioned shortness of breath as a possible side-effect of bretylium tosylate therapy. This is difficult to evaluate, as coexisting left ventricular failure is common in hypertensives, but we would confirm the impression that dyspnoea on effort would seem in a few cases to be unrelated to deterioration in cardiac function. We have never observed the radiological appearances of the "hexamethonium lung" nor the appearance of Kerley's subpleural lines which might be expected in the long run if chronic pulmonary oedema ensued, as Turner and Lowther suggest.

Discussion

Since June, 1959, when the first results of treatment with bretylium tosylate were reported from University College (Boura *et al.*, 1959), further reports have appeared from Smirk and Hodge (1959), Dollery *et al.* (1960), Turner and Lowther (1960), and Evanson and Sears (1960), most of them embodying an experience of approximately six months' treatment. Our experience dates from June, 1959, when we received the first consignments of the drug from the Wellcome Foundation. On the whole we would agree with the findings of the other authors that bretylium tosylate is an important advance in the treatment of severe hypertension, but that it must be regarded as a drug not easy to handle with potential dangers. The dangers are mainly due to irregularity in absorption, clearly demonstrated by the labelled isotope studies from Hammersmith, and this may cause unpredictable sudden hypotensive crises, especially under the influence of physical effort, with consequent vascular occlusions in vital territories. The sharpness of orthostatic hypotension can be compared to that obtained with parenteral hexamethonium and pentolinium; we were therefore not surprised to find five patients who developed pain in the nape, three of whom had experienced similar symptoms while on parenteral pentolinium.

Because of this it is doubtful whether bretylium tosylate should ever be used in the presence of cerebral vascular disease. If recourse to powerful hypotensive agents is imperative in such cases, then the better-absorbed drugs with more predictable action, such as mecamylamine or pempidine, seem preferable. Bretylium tosylate has a very slight hypotensive action in the supine posture, and for this reason we have found it of little use in the treatment of patients confined to bed, such as in acute left ventricular failure, subarachnoid haemorrhage with severe hypertension, and severe toxaemia of pregnancy. In these cases we still favour the use of parenteral pentolinium. Uncomplicated essential hypertension in pregnancy can instead be successfully treated with bretylium tosylate, as the patient can be allowed to be ambulant.

We cannot agree with the Hammersmith and Edinburgh workers that the hypotensive response to bretylium tosylate is poor in malignant and severe hypertension with retinal exudates; in our experience the response is just as unpredictable as with ganglion-blocking agents, and in the first stages of treatment we found that orthostatic hypotension often ensued with doses of only 100 mg. t.i.d. We have found, however, that tolerance develops rather rapidly in these patients, so that the final stable dose is high.

Contrary to the experience of Dollery *et al.* (1960), we have found that the addition of an oral diuretic of the benzothiadiazine series will usually potentiate the hypotensive action of bretylium tosylate (Montuschi, 1959). We have used hydroflumethiazide for this purpose, and in 20 of our cases it has proved of great value in achieving control without the general inconvenience and liability to side-effects of the high dosage of bretylium that would otherwise have been needed. A morning dose of 100 mg. of the diuretic usually suffices.

With this exception we have little experience of the combined action of bretylium tosylate with other drugs. The addition of pempidine or of trimethidinium in a very few cases seemed to confirm the favourable findings of Smirk and Hodge (1959), and we feel that the whole question of combined treatment with modern hypotensive drugs requires further study. For example, as bretylium increases the sensitivity of the blood-vessels to circulating noradrenaline, it would be of great interest to observe whether the addition of an adrenalytic agent would help in the control or resistant cases.

The mechanism of the minor but annoying side-effects that interfere with the usefulness of this valuable drug also requires further investigation. Although Boura *et al.* (1959) claimed that it has no central action, a severe general asthenia with tremor of the limbs recalling the central effect of mecamylamine occurred in one of our patients one week after she had changed from pentolinium to bretylium tosylate, the symptoms ceasing immediately on reversion to the former treatment. Evanson (personal communication) reports dysarthria associated with severe general muscular weakness in another case.

So far there has been no evidence of a toxic action on the liver, kidneys, or the haemopoietic system, and none of our patients has developed a dissecting aneurysm (Beaven and Murphy, 1956).

The freedom from the more serious side-effects consequent on parasympathetic blockade and depressant central action of other drugs is a conspicuous advantage in the use of bretylium tosylate, and many patients, especially those on high dosage, were most grateful for this relief. As will be seen from Table II, satisfactory and uneventful control of the blood-pressure has been achieved in 71% of our cases, and it must be emphasized that no case of mild or moderate hypertension has been included. We feel, indeed, that bretylium tosylate, with its powerful and sometimes unpredictable action, is out of place in dealing with uncomplicated moderate benign hypertension, especially if the patient is leading an active life.

Judged by the yardstick of its effectiveness in malignant hypertension, this drug has given an encouraging success rate of just over 50% during a period of six to nine months. It is without doubt an important advance in the treatment of severe hypertension.

Summary and Conclusions

By its selective action in blocking the peripheral sympathetic nerves without interfering with parasympathetic transmission, bretylium tosylate offers a new type of treatment in hypertensive disease that is free from some of the serious disadvantages of its predecessors.

Using this drug in 75 cases of severe hypertension over a period of nine months, we have obtained successful control in 71%, including 7 out of 13 cases of malignant hypertension.

The main disadvantages in its clinical use appear to stem from a marked variability in its absorption from the digestive tract. This may lead on the one hand to severe postural hypotension on low dosage or on the other to the necessity for very large doses which expose the patient to a number of minor side-effects. This effect can be countered to some extent by the adjuvant action of hydroflumethiazide. The frequent occurrence of postural hypotension after physical effort in patients taking this drug makes it unsuitable for the treatment of uncomplicated moderate benign hypertension in active subjects. Its mode of action also makes it ineffective in the recumbent patient.

Administration of bretylium tosylate requires careful supervision, as a collapse of the blood-pressure with fainting is not uncommon when the drug is first introduced, and may occur unexpectedly later. For this reason we do not recommend its use in patients with established coronary or cerebral vascular disease.

We thank Dr. David Long, of the Wellcome Foundation, for supplies of bretylium tosylate (darenthin).

References

Arnold, P., and Rosenheim, M. L. (1949). *Lancet*, **2**, 321.
Beaven, D. W., and Murphy, E. A. (1956). *Brit. med. J.*, **1**, 77.
Bennett, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, **2**, 218.
Boura, A. L. A., and Green, A. F. (1959). *Brit. J. Pharmacol.*, **14**, 536.
—— —— McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
Dollery, C. T., Emslie-Smith, D., and McMichael, J. (1960). Ibid., **1**, 296.
Evanson, J. M., and Sears, H. T. N. (1960). Ibid., **1**, 544.
Harington, M., Kincaid-Smith, P., and McMichael, J. (1959). *Brit. med. J.*, **2**, 969.
Le Quesne, L. P., Hobsley, M., and Hand, B. H. (1960). Ibid., **1**, 141.
Lowe, R. D., and Rosenheim, M. L. (1960). *Lancet*, **1**, 655.
Montuschi, E. (1957). *Proc. roy. Soc. Med.*, **50**, 514.
—— (1959). *Lancet*, **2**, 462.
Smirk, F. H., and Hodge, J. V. (1959). Ibid., **2**, 673.
Turner, R., and Lowther, C. (1960). Ibid., **1**, 381.

DRUG PROPHYLAXIS IN MIGRAINE

A CONTROLLED CLINICAL TRIAL

BY

RODNEY GRAHAME, M.B., B.S., M.R.C.P.

Formerly Captain, R.A.M.C.; Junior Specialist in Medicine

From the Cambridge Military Hospital, Aldershot

Migraine, in common with other psychosomatic diseases, is subject to wide variation in severity during the patient's lifetime. The condition is exacerbated under the influence of adverse physical and psychological factors, and it is common experience that relief from these is sufficient in many patients to produce a remission. It follows, therefore, that assessment of any form of drug therapy aimed at the prevention or modification of attacks is beset with obvious practical difficulties; for not only is the disease influenced by many variable factors but also, as Graham (1956) has pointed out, it is "notorious for responding temporarily to any new and encouraging form of therapy."

It is therefore essential that any attempt to demonstrate the effect of drug treatment in migraine must be made with full statistical control by applying the technique of the double-blind trial.

Current Views

The idea that reserpine, an alkaloid contained in *Rauwolfia serpentina*, might be employed in the preventive treatment of migraine arose from light that has been shed on its pharmacology by recent research. Known and used in the Orient for centuries, and in recent years achieving universal use in the treatment of hypertension and a variety of psychiatric disorders, reserpine was thought to exert its effect on the central nervous system (Bein, 1953).

It has become increasingly clear since experiments initially conducted on rabbits and later applied to man by McQueen *et al.* (1955) that the peripheral vasodilatation is in part effected by direct action. Maxwell *et al.* (1956, 1957) concluded, using anaesthetized dogs premedicated with a ganglion-blocking agent, that the response to reserpine was by direct peripheral action on the vessels, and suggested an adrenaline release. Since then it has been conclusively demonstrated that reserpine depletes adrenaline and noradrenaline stores (Kroneberg and Schümann, 1957, 1958) in the adrenal gland (Carlsson and Hillarp, 1956; Mirkin, 1958; Molinatti *et al.*, 1958; Camanni and Molinatti, 1958; Camanni *et al.*, 1958), arterial wall (Burn and Rand, 1957, 1958), blood (Burger, 1956), brain (Holzbauer and Vogt, 1956; Brodie *et al.*, 1957; Shore *et al.*, 1957), sympathetic ganglia (Muscholl and Vogt, 1958), and the heart (Bertler *et al.*, 1956). Similarly, serotonin is released from a variety of different tissues, including the brain (Brodie *et al.*, 1957) and the intestine (Fletscher *et al.*, 1955).

In view of their finding of catechol amine release from arterial walls after the administration of reserpine, Burn and Rand suggested that this discovery might have clinical application in various disorders where the underlying mechanism is a paroxysmal vasoconstriction. Yet in studying the literature it is apparent that very little work has been done in this field. Scalfi *et al.* (1956) treated some 14 patients suffering from various disorders of the peripheral vasculature (including four with Raynaud's disease) with reserpine and, using photoplethysmography, noted an objective improvement in nine (including three of the patients with Raynaud's disease).

Friedman (1955) treated with reserpine 58 patients suffering from migraine, and only 22 of them showed an appreciable improvement. Of 12 patients given a control tablet, seven improved. Barrett and Hansel (1955) treated 21 patients suffering from various kinds of headache (including two with migraine) in an uncontrolled trial, and concluded that "reserpine appears to be effective in all vascular headaches regardless of their basic mechanism."

The value of sedatives alone in the prophylaxis of migraine has been pointed out by Kunkle and Wolff (1951), and in particular phenobarbitone has been strongly advocated by Brain (1951).

It was therefore decided to assess the relative merits of reserpine and phenobarbitone in the prevention of migraine attacks by comparing their effect with that of a placebo and with that of no treatment at all.

Patients Investigated

In January, 1959, a migraine clinic was set up at the Cambridge Military Hospital in order to conduct the trial. All medical officers in the Aldershot area were requested to refer suitable patients, and of those interviewed, 43 were originally regarded as suitable. Criteria for inclusion were strict, and the decision rested on a firm diagnosis of migraine coupled with a high order of frequency of attack at the commencement of the trial. In 15 cases the six-months trial period was not completed. In some instances this was because the men were posted away from the area. The remainder withdrew at their own request.

Twenty-eight patients (26 males and 2 females) completed the six-months observation period, the women being wives of serving soldiers. The ages varied from 15 to 46 years, average 23.8 years. Details of the group are as follows:

Age distribution	15– 9	20– 11	25– 3	30– 1	35– 2	40– 1	45–49 1
Rank	Boys 2		Privates 16		N.C.O.s 6		Officers 2
Length of service	< 1 year 17		1–2 years 5		10–20 years 4		
Enlistment	Regular 6		Short service 1		Nat. Service 17		Boy soldiers 2

At the initial visit a full history and clinical examination was undertaken. Physical examination, which included blood-pressure estimation and listening for an intracranial bruit, did not reveal any abnormality.

The headache was unilateral in 25 cases and bilateral in three. Of the former, 21 experienced the attack on one side only, the other four being affected on either side, with a predilection for one side in three of these. Of the 21 patients who were able to locate the onset of the pain, the sites were: frontal, 9; retro-orbital, 8; temporal, 3; and occipital, 1.

Nausea was experienced in 23 patients and was severe in 12. Vomiting occurred invariably in 10 patients and occasionally in a further five. It was absent in 13.

Of the visual disturbances, the characteristic fortification spectra were experienced in 17 patients; photophobia was severe in 18 cases; and significant blurring of vision occurred in five. Field effects occurred in five patients (homonymous hemianopia in four, and bitemporal hemianopia in one). Other focal neurological symptoms were encountered, four patients complaining of focal numbness, three of focal paraesthesiae, one of focal pain, and two experienced transient hyperacusis. Complete absence of visual or neurological symptoms with the onset of the attack occurred in only one patient.

A possible relevant past history was forthcoming in only three patients (meningitis, head injury, and "nervous breakdown" in one each). A family history of migraine was elicited in 13 patients (mother in nine, father in one, aunt in two, and grandmother in one).

The frequency of attack at the onset of the trial was one or more per week in 22 cases, and between one and three per month in the remainder.

An inquiry into previous treatment revealed that five had had no previous medical treatment, 14 had been treated with ergotamine, nine with phenobarbitone, four with aspirin, and one with pethidine.

All patients were asked to mention any precipitating factors: nine mentioned anxiety, two relaxation, three travel, five concentration or study, five physical exertion, and one constipation.

Method

In the first half of the trial the patient's response to maintenance therapy with reserpine (0.25 mg. three times daily after meals) over a six-weeks period was compared with that of an identical inert tablet over the same period of time. Thus the patient was acting as his own control. Half the patients received reserpine over the first period, the other half receiving the placebo. Random selection of cards from a pack determined whether the patient began with the drug or the placebo. At the end of six weeks, those who had been given the reserpine were switched to the control, and vice versa. The identity of the tablets that the patients were receiving during this half of the trial was closely guarded by the pharmacists from me until the trial was

completed. Each patient was seen in the clinic at fortnightly intervals to record progress and to keep a watch for the possible appearance of toxic manifestations.

At the end of this half of the trial each patient was given a third yet identical tablet containing phenobarbitone (¼ gr. (32 mg.) three times daily, after meals) and the progress recorded. In the final six-weeks period the patient was observed while receiving no maintenance therapy. During the whole period under trial the patients were asked to note in a diary each attack as it occurred, and in this way an accurate record of both frequency and severity of the migraine attacks was available. In view of the fact that this was an evaluation of prevention of attacks, no special restrictions were placed on symptomatic treatment of the individual migraine headache with aspirin, codeine, or ergotamine tartrate. The patients' medical officers were requested to refrain from prescribing any other regular treatment, particularly barbiturates, during the trial. Clearly, as in any investigation of this nature, one had to place complete reliance on the patients to take their prescribed tablets. It should be pointed out, however, that in the present trial there was no instance in which there was the slightest reason to doubt the patient's integrity.

Results

Reserpine and Placebo

The number of migraine headaches experienced by the individual patients during the first half of the trial are recorded in Table I. The numbers in parentheses refer to mild attacks.

TABLE I

Case	Reserpine	Placebo	Case	Reserpine	Placebo
1	0	4	15	16	17
2	0 (1)	0 (2)	16	2 (1)	10 (3)
3	3 (2)	1 (1)	17	4 (1)	1 (2)
4	0	4	18	0	2
5	0 (1)	3	19	1 (1)	2 (6)
6	0 (2)	0 (4)	20	2 (4)	9
7	29	21	21	42	41
8	2	4	22	1	0
9	0	0 (2)	23	1	1 (5)
10	13	15	24	22	21
11	0	7	25	8	6
12	1 (1)	1	26	4 (2)	5 (1)
13	2 (5)	7 (2)	27	3	8
14	7 (2)	6	28	7 (1)	7 (1)

It will be appreciated that this half of the trial represents the fully randomized part of the investigation. It follows, therefore, that it is the only part of the trial that would be likely to yield any statistically valid comparisons.

The choice of the most suitable method of interpretation of the results posed a problem. At first sight it might appear that a formal "t" test using the differences in the numbers of headaches should be adopted. However, because the sample consisted of patients with such a wide variation in the number of attacks, those with the largest numbers would give undue bias to the results as a whole. For example, Patient No. 7 experienced 29 attacks while on reserpine compared with 21 on the placebo. Though his frequency of attack was reduced on the latter by only 36%, by virtue of the numerical difference of eight he would effectively cancel out, say, Patients Nos. 1 and 4, both of whom were kept free of migraine while receiving reserpine. In view of this tendency the "t" test was not regarded as appropriate for this type of sample.

Instead, the degree of improvement derived from reserpine as compared with placebo, or vice versa, was expressed as a percentage reduction in frequency of attack. Since a prophylactic drug that failed to reduce the frequency by one-half was unlikely to be of much clinical value, *the chosen arbitrary criterion of improvement was a reduction of 50% or more in the frequency of attack.* Anything less than 50% was regarded as unchanged. For the purposes of calculation a mild attack was counted as being equivalent to one-half of a severe one.

If these criteria were applied to the results the following observations may be made.

Comparison of reserpine with the placebo (crossover trial) showed:

Improved by reserpine	14 (50%)
Improved by placebo	3 (10.7%)
Unchanged	11 (39.3%)
	28 (100%)

If this result is applied to the significance chart for percentages devised by Rosenbaum (1959) the difference between reserpine and the placebo is significant at the 5% level of significance.

Phenobarbitone and Placebo

In the third six-weeks period all patients received phenobarbitone. The number of attacks occurring in this period is shown in Table II. For the purposes of comparison the corresponding numbers relating to the period on the placebo are also shown. Patients Nos. 13 and 27 were posted away from the area, so that their response to phenobarbitone could not be tested. As they both had already provided useful information in the remainder of the trial, it was not thought justifiable to reject them. In both cases the results relating to the final stage were later made available by letter.

TABLE II

Case	Pheno-barbitone	Placebo	Case	Pheno-barbitone	Placebo
1	0	4	15	19	17
2	1	0 (2)	16	2	10 (3)
3	0	1 (1)	17	3	1 (2)
4	0 (1)	4	18	0	2
5	0 (1)	3	19	1 (2)	2 (6)
6	2	0 (4)	20	3 (6)	9
7	23	21	21	41	41
8	4	4	22	0	0
9	1	0 (2)	23	0	1 (5)
10	11	15	24	22	21
11	0	7	25	12	6
12	0	1	26	3 (1)	5 (1)
13	—	7 (2)	27	—	8
14	10	6	28	1 (1)	7 (1)

Comparison of the placebo with phenobarbitone after a period of time had elapsed (six weeks in half the patients and three months in the remainder) showed:

Improved by placebo	1 (3.85%)
Improved by phenobarbitone	11 (42.3%)
Unchanged	14 (53.85%)
	26 (100%)

The difference is significant at the 5% level of significance and could be a true effect. Since the two phases of treatment bore a constant time-relationship with each other and not a randomized one, the result could also be due to the passage of time.

Placebo and No Treatment

The results of the final phase of the trial are shown in Table III, together with the corresponding results relating to the placebo.

Table III

Case	No Treatment	Placebo	Case	No Treatment	Placebo
1	2	4	15	3	17
2	2	0 (2)	16	0 (6)	10 (3)
3	1 (1)	1 (1)	17	5	1 (2)
4	0	4	18	0	2
5	1	3	19	3 (1)	2 (6)
6	1	0 (4)	20	7	9
7	3 (5)	21	21	5 (16)	41
8	5	4	22	0	0
9	0	0 (2)	23	4	1 (5)
10	7	15	24	20	21
11	0	7	25	12	6
12	1	1	26	1 (3)	5 (1)
13	4	7 (2)	27	5	8
14	8	6	28	5	7 (1)

Comparison of the placebo with no treatment after a period of time (either three months or four-and-a-half months) showed:

Improved by placebo	3 (10.7%)
Improved by no treatment	14 (50%)
Unchanged	11 (39.3%)
	28 (100%)

The result is statistically significant at the 5% level of significance, and similarly could be a true effect or be due to the effect of the passage of time.

Other Comparisons

The other possible comparisons—namely, phenobarbitone with no treatment, reserpine with no treatment, and reserpine with phenobarbitone—do not reveal any significant differences.

If the combined reserpine and phenobarbitone results are compared with those with the placebo, and the most favourable drug is taken in each case, the following observations may be made.

Improved by reserpine or phenobarbitone	16 (57.2%)
Improved by placebo	0
Unchanged	12 (42.8%)

This result is significant at the 1% level of significance, though, as before, when phenobarbitone is taken the possibility that the effective improvement could be due to the passage of time cannot be ruled out.

Side-effects

Side-effects were noted in 13 patients at some time during the trial. Without exception they were trivial in nature and tended to occur during the first days of treatment. In no case was it necessary to interrupt the trial on their account. In fact, they were rather more common with the control than with either of the drugs. They may be summarized as follows:

Reserpine.—Mild depression, 1; mild indigestion, 1; feeling of well-being, 1; feeling "shaky," 1; nasal congestion, 1; slight dazed feeling, 1.

Phenobarbitone.—Slight dizziness, 1; tiredness, 2.

Placebo.—Mild depression, 1; dizziness on rising, 2; feeling on edge, 2; slight ingestion, 1; feeling tired, 2; bad dreams, 1.

Discussion

It will be appreciated that this series differs in two important respects from a completely unselected series of patients suffering from migraine. Firstly, there was an overwhelming preponderance of males (93%) in a disorder where 70% of the sufferers are female. Secondly, there was a high order of frequency of attack—namely, 21% experienced attacks less often than once a week compared with 55% in an unselected series (Friedman *et al.*, 1954). While the former discrepancy was unavoidable in a Service population, the latter was deliberate because of the limited duration of the trial.

The results suggest that both reserpine and phenobarbitone are of value in reducing the frequency of migraine in certain patients as compared with a dummy tablet. In this trial the proportions improved were 50% and 42.3% respectively. With regard to the reserpine the effect is a true one, whereas with phenobarbitone, because its administration was not randomized, the effect could be due to the passage of time. However, as there is no apparent reason why such a large number of patients should all develop a remission at that time, the effect is likely to be a true one.

It is further suggested that a larger percentage of migraine sufferers (in this trial 57.2%) might benefit from one or other of these two drugs administered over different periods. It is observed that of the 15 not improved by phenobarbitone, five were improved by reserpine; and of the 14 unchanged by reserpine, three improved on phenobarbitone. A point of interest is that among 10 patients unresponsive to either form of therapy were the five most severe cases, these experiencing between two and seven attacks a week.

It is perhaps surprising to find that patients were worse on the placebo tablet and when they received no maintenance therapy. Again this could possibly be a time effect, and, for the same reasons mentioned above in connexion with phenobarbitone, this cannot be ruled out. Should it be a true effect it would appear to produce the opposite result to the one expected. Possibly the mere taking of frequent tablets, constantly reminding the patient of his complaint, might be the mechanism of the increased frequency. This might also explain the increase of reported side-effects with the placebo. The coinciding of the onset of the warm summer of 1959 with the final stage of the trial is another possible explanation of the general improvement.

It is not possible to comment on the basis of this work or whether the beneficial effect of reserpine in migraine is mediated through its central sedative action or through its effect of catechol amine release from peripheral arterial walls.

Summary

In a controlled clinical trial the response of 28 patients suffering from severe migraine to prophylactic maintenance therapy with reserpine, phenobarbitone, and a placebo tablet was assessed. The response to reserpine and phenobarbitone was favourable in 14 and 11 patients respectively. 16 patients were improved with one of the two drugs administered over different periods. There was a slight increase in the severity of the condition using a placebo compared with that observed without maintenance therapy.

The recent pharmacology of reserpine is reviewed.

I am indebted to Dr. A. Barham Carter, Adviser in Neurology at the War Office, for his encouragement and guidance in the preparation of this trial and paper; to Mr. S. Rosenbaum, of the War Office, for statistical advice; to the Commanding Officer and pharmacists of the Cambridge Military Hospital for their invaluable co-operation; and to Messrs. British Drug Houses for generous supplies of the tablets specially prepared for use in this trial.

REFERENCES

Barrett, B. M., and Hansel, F. K. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 250.
Bein, H. J. (1953). *Experientia (Basel)*, **9**, 107.
Bertler, A., Carlsson, A., and Rosengren, E. (1956). *Naturwissenschaften*, **43**, 521.
Brain, R. (1951). *Diseases of the Nervous System*, 4th ed. Oxf. Med. Publ., London.
Brodie, B. B., Olin, J. S., Kuntzman, R. G., and Shore, P. A. (1957). *Science*, **125**, 1293.
Burger, M. (1956). *Helv. physiol. pharmacol. Acta*, **14**, C. 13.
Burn, J. H., and Rand, M. J. (1957). *Lancet*, **2**, 1097.
—— —— (1958). *Brit. med. J.*, **1**, 903.
Camanni, F., Losana, O., and Molinatti, G. M. (1958). *Experientia (Basel)*, **14**, 199.
—— and Molinatti, G. M. (1958). *Acta endocr. (Kbh.)*, **29**, 369.
Carlsson, A., and Hillarp, N. A. (1956). *K. fysiogr. Sällsk. Lund Förh.*, **26**, 8.
Fletscher, A., Shore, P. A., and Brodie, B. B. (1955). *Science*, **122**, 374.
Friedman, A. P. (1955). *Neurology*, **5**, 805.
—— von Storch, T. J. C., and Merritt, H. H. (1954). Ibid., **4**, 773.
Graham, J. R. (1956). *Treatment of Migraine*, Little, Brown, Boston.
Holzbauer, M., and Vogt, M. (1956). *J. Neurochem.*, **1**, 8.
Kroneberg, G., and Schümann, H. J. (1957). *Arzneimittel-Forsch.*, **7**, 279.
—— —— (1958). *Arch. exp. Path. Pharmakol.*, **234**, 133.
Kunkle, E. C., and Wolff, H. G. (1951). In *Modern Trends in Neurology*, edited by A. Feiling. Butterworth, London.
McQueen, E. G., Doyle, A. E., and Smirk, F. H. (1955). *Circulation*, **11**, 161.
Maxwell, R. A., Plummer, A. J., Osborne, M. W., and Ross, S. (1956). *J. Pharmacol.*, **116**, 42.
—— Ross, S. D., Plummer, A. J., and Sigg, E. B. (1957). Ibid., **119**, 69.
Mirkin, B. L. (1958). *Nature (Lond.)*, **182**, 113.
Molinatti, G. M., Camanni, F., and Losana, O. (1958). *Arch. int. Pharmacodyn.*, **116**, 483.
Muscholl, E., and Vogt, M. (1958). *J. Physiol. (Lond.)*, **141**, 132.
Rosenbaum, S. (1959). *Appl. Statist.*, **8**, 45.
Scalfi, L., Jacono, A., and Iuliani, G. (1956). *G. Clin. med. (Parma)*, **37**, 1635.
Shore, P. A., Olin, J. S., and Brodie, B. B. (1957). *Fed. Proc.*, **16**, 335.

Preliminary Communications

Ethionamide

The Clinical Trials Committee of the Research Committee of the British Tuberculosis Association has for the past 12 months been investigating the use of ethionamide (2-ethylthio*iso*nicotinamide; "1314") with cycloserine or pyrazinamide in patients with advanced pulmonary tuberculosis in whom treatment with streptomycin, P.A.S., and isoniazid has failed. The results will be published in full when the study has been completed; but some important findings have already emerged and justify a preliminary report at this early stage.

Treatment.—All patients have been treated initially in hospital. None of them have previously received the two drugs with which they were treated in this investigation. They have received 500 mg. of ethionamide daily in two doses of 250 mg. in enteric-coated tablets morning and evening, with either cycloserine (0.5 to 1 g., according to body weight in two equal doses daily) or pyrazinamide (2–3 g., according to body weight in two equal doses daily).

Bacterial Resistance.—All resistance tests have been carried out in the same laboratory.

Sensitivity Before Treatment.—Sensitivity tests have been done on pretreatment cultures from 26 patients in the pyrazinamide/ethionamide group. The cultures obtained from two patients had resistance ratios (R.R.)* to ethionamide of 4 and 8 respectively; the cultures were sensitive to pyrazinamide (R.R. $\frac{1}{4}$ and $\frac{1}{2}$). They were treated with ethionamide and pyrazinamide, and in both cases sputum remained positive and the cultures became less sensitive to pyrazinamide (R.R. >8, >16). The cultures from three patients had resistance ratios to pyrazinamide of 4, >16, and 32 respectively, but were sensitive to ethionamide (R.R. 1 in each case). They were treated with ethionamide and pyrazinamide, and in all three cases the sputum remained positive and the cultures became less sensitive to ethionamide (R.R. 16, >8, 32).

Sensitivity tests have been done on pretreatment cultures from 20 patients in the cycloserine/ethionamide group. No cultures had resistance ratios of 4 or more to either cycloserine or ethionamide.

Sensitivity During Treatment.—Cultures with resistance ratios of 4 or more have so far been obtained at some stage of treatment in 10 out of 29 patients in the pyrazinamide group. Decreased sensitivity to pyrazinamide has appeared in nine cases and to ethionamide in five; in most cases change of pyrazinamide sensitivity has appeared first. In the cycloserine group there has been no apparent change in cycloserine sensitivity of any of the cultures; but cultures with decreased ethionamide sensitivity have appeared in 9 out of 23 patients.

In both treatment groups some of the patients from whom resistant cultures had been obtained have later had negative cultures.

Changes in Bacillary Content of the Sputum.—In the pyrazinamide group 13 out of 25 patients had a negative culture at the end of the third month and 8 out of 15 at the end of the sixth month. The corresponding figures in the cycloserine group were 18 out of 21 and 7 out of 11. So far nine of the pyrazinamide and seven of the cycloserine group have had negative cultures for one month or more.

Drug Intolerance.—Gastro-intestinal symptoms attributed to ethionamide have caused interruptions of treatment in many of the patients, and two had to stop treatment entirely because of them. Cycloserine toxicity in two patients and hepatitis attributed to pyrazinamide in six patients have resulted in these eight patients having to stop treatment.

CONCLUSIONS

The investigation was not designed to compare the results of treatment with certain doses of ethionamide and cycloserine and of ethionamide and pyrazinamide. The patients were not randomly allocated to the treatment groups, and from the information at present available it is not known how similar the groups were. It is not justified to compare the results with published results of treatment with cycloserine or pyrazinamide and other drugs. It seems, however, reasonable to draw the following conclusions from this preliminary analysis.

1. Cultures from patients who have not previously received either pyrazinamide or ethionamide may have decreased sensitivity to one or other of them. In such patients, treatment with either drug in combination with another may be unsuccessful and lead to resistance to the companion drug. Whenever possible, therefore, it is desirable to wait for the results of sensitivity tests before starting treatment with either pyrazinamide or ethionamide.

*Resistance ratio is the ratio of the minimum inhibitory concentration of the drug for the test organism to that for the standard sensitive strain (*Myco. tuberculosis* $H_{37}Rv$).

2. The doses of cycloserine (0.5–1 g.) used in this investigation appeared to be inadequate to protect completely against the emergence of cultures with decreased sensitivity to ethionamide; and the dose of ethionamide (500 mg.) appeared insufficient completely to prevent decrease of pyrazinamide sensitivity.

The patients all had advanced disease with tubercle bacilli persisting in the sputum after treatment for long periods with other drug combinations. About one-third of them have become sputum-negative on culture for at least one month. Some may relapse later; but these early good results, though admittedly few, suggest that further clinical investigation of ethionamide is desirable. The Research Committee of the British Tuberculosis Association is now investigating the drug more fully.

The patients have been under the care of a number of physicians, for whose co-operation the Research Committee is grateful. The Committee also thanks Miss Eileen Hall for her valuable help with the sensitivity testing. The investigation was begun at the request of May and Baker Limited.

R. W. Riddell, M.D., F.R.C.P.Ed.,
Chairman.
Sheila M. Stewart, B.Sc., Ph.D.,
Bacteriologist.
A. R. Somner, M.D., M.R.C.P.Ed.,
Co-ordinator.
Clinical Trials Committee of the Research Committee of the British Tuberculosis Association.

Medical Memoranda

Metastatic Carcinoma at the Site of Injection of Penicillin

The recent report (Crowley and Still, 1960) of a case showing a metastasis from carcinoma of the cervix at the site of intramuscular injections of iron-dextran complex prompts us to report a case in which metastasis occurred at the site of intramuscular penicillin injections.

Case History

A 65-year-old man was admitted for investigation of an opacity found on routine chest *x*-ray examination. A lobectomy was performed on July 15, 1957, and histological examination of the specimen showed a poorly differentiated squamous-cell carcinoma with no evidence of regional lymph-node involvement. Injections of soluble penicillin to a total of 46 million units were given into both buttocks between July 8 and 22. Subsequently a course of deep *x*-ray therapy was given to the mediastinum.

In January, 1958, he was found to have a tender, fluctuant swelling four inches (10 cm.) in diameter in the upper part of the right buttock. Incision revealed a cavity in the gluteus maximus muscle containing blood-stained fluid, and section of tissue from its wall showed fibrous tissue with clumps of carcinoma cells identical in appearance to those of the primary bronchial tumour. The lesion was widely excised and a course of deep *x*-ray therapy to this area was begun, but he died of widespread disease on April 7.

Post-mortem examination (Dr. R. E. Cotton) showed metastases in mediastinal lymph nodes, lung, pleura, myocardium, suprarenals, kidneys, and liver. Neoplasm was still present in the gluteus maximus muscle and subcutaneous deposits had developed around the scar. No other metastases in muscle were found.

Comment

Reports of metastases to skeletal muscle from neoplasms at any site are uncommon. Willis (1952) reports four cases in a personal series of 500 necropsies, none of them from carcinoma of the bronchus. In a review of 3,047 cases of carcinoma of the bronchus Ochsner and DeBakey (1942) state that haematogenous metastasis to skeletal muscles occurred very rarely, but give no figure for its relative incidence. We have been able to find only two case reports of such spread from carcinoma of the bronchus. Handford (1888) reported a case of "mediastinal carcinoma" (which, from its description, appears to have been a case of carcinoma of the bronchus) in which metastases occurred in the right deltoid and in the muscles of the left thigh. In the other case (Atkin, 1931) a metastasis was found in the peroneus longus muscle.

While the animal experiments of Richmond (1959) and Haddow and Horning (1960) have shown the carcinogenic effects of iron-dextran complex given either intramuscularly or subcutaneously, the doses used were proportionately much greater than those used therapeutically. On the other hand, local tissue damage is recognized as predisposing to metastasis. Willis (1952) records three cases of metastasis to injured or diseased tissue from various primary sites. In the present case, and in that reported by Crowley and Still (1960), it would seem probable that the occurrence of metastases at the site of intramuscular injections was the result of tissue damage rather than a specific effect of the substances injected.

We wish to thank Mr. J. Belcher, Mr. J. H. L. Ferguson, and Miss M. D. Snelling for permission to publish this case, and Dr. R. E. Cotton and Dr. A. D. Thomson for the histological and post-mortem reports.

T. S. Worthy, Ph.D., M.B., B.Chir., D.M.R.T.,
Registrar, The Meyerstein Institute of Radiotherapy, The Middlesex Hospital.
E. J. C. Wynne, M.A., M.Chir., M.B., F.R.C.S.,
Senior Surgical Registrar, The Middlesex Hospital.

References

Atkin, E. E. (1931). *J. Path. Bact.*, **34**, 343.
Crowley, J. D., and Still, W. J. S. (1960). *Brit. med. J.*, **1**, 1411.
Haddow, A., and Horning, E. S. (1960). *J. nat. Cancer Inst.*, **24**, 109.
Handford, H. (1888). *Trans. path. Soc. Lond.*, **39**, 48.
Ochsner, A., and DeBakey, M. (1942). *J. thorac. Surg.*, **11**, 357.
Richmond, H. G. (1959). *Brit. med. J.*, **1**, 947.
Willis, R. A. (1952). *The Spread of Tumours in the Human Body*, 2nd ed., pp. 285 and 299. Butterworth, London.

"A report by the Paris prefect of police and the prefect of the Seine department shows that air pollution has tripled in Paris during the past 50 years, and that 45% of this increase can be attributed to motor traffic. It is stated that domestic central heating is responsible for a large proportion of the SO_2 in the air, rising to 88% of the total during the winter. The prefects' report warns that many of the street trees in the city will be dead by the end of the century if nothing is done. The remedies are regarded as being to reduce the sulphur content of solid and liquid fuels as much as possible, and to extend district heating systems, thereby reducing the number of individual installations. New clean-air legislation for France is under consideration, which, in addition to providing for stricter control over heating installations, would also control the pollution from road vehicles, including the output of carbon monoxide, and provisions for the immobilization of diesel vehicles producing excessive smoke." (*Journal of the National Society for Clean Air*, Autumn, 1960.)

Reviews

BIOCHEMICAL GENETICS

Human Biochemical Genetics. By H. Harris. Foreword by L. S. Penrose, F.R.S. (Pp. 310+viii; illustrated. 37s. 6d.) London: Cambridge University Press. 1959.

Progress in human biochemical genetics has been so rapid that pace had to be kept by publishing reviews of selected subjects and by the most comprehensive catalogues. We have now been presented with the first comprehensive textbook which attempts to systematize the whole field. As a textbook should, it confines itself to consolidated knowledge; and the temptation to indulge in speculation, fascinating as some might be, is resisted with almost puritan sobriety. In fact, sometimes caution goes a little too far: the human gamete is "now thought" to contain 23 chromosomes; in primaquine sensitivity the red cell defect is "probably" based on a genetically determined deficiency of glucose-6-phosphate dehydrogenase. A most instructive table listing sixteen inherited enzyme deficiencies, of which ten have been demonstrated directly *in vitro*, is entitled "probable deficiency . . ."

There are two general introductory chapters and a chapter at the end which deals with gene action. The first two explain principles of genetics—chromosomes, genes, consanguinity, heterozygotes and homozygotes, sex linkage. The final chapter discusses the relation of genes to proteins and the gene-enzyme hypothesis. It includes a singularly well-written account of the Watson-Crick formulation of the chemical structure of D.N.A. and how this can account for certain characteristics of genes and chromosomes.

There are two chapters on amino-acid metabolism, a field in which the author himself has made so many distinguished contributions. Variations in carbohydrate metabolism include glycogen-storage disease, renal glycosuria, galactosaemia, and primaquine sensitivity of red cells. It is now accepted that there exist a whole series of inherited glycogen-storage diseases. The various stages of glycogen breakdown from the outer to the inner branches of the chains of glucose units which form the molecular "tree" to the final dephosphorylation of glucose-6-phosphate may nearly all be involved. Similarly renal glycosuria may either be of the type where the mean threshold of the nephrons is lower than normal, or be associated with a normal mean threshold with a lowered minimal threshold. The largest single subject is the haemoglobins. It is here that Ingram's work has gone furthest in linking genetical variation with chemical structure and where balanced polymorphism is illustrated by the maintenance of the sickling gene at high frequency by the protection of sickling heterozygotes against malaria. Blood group substances and plasma proteins are of course of particular interest to the biochemist. The genetics of plasma proteins have now involved the different haptoglobins, β and γ globulins, pseudocholinesterases, deficiencies of caeruloplasmin, fibrinogen, the haemophilias, and other coagulation defects. These different factors have in common only that they are all present in the plasma, yet this chapter has welded them together so that the reader can approach them as one subject. The largest chapter deals with miscellaneous problems: the porphyrias, congenital hyperbilirubinaemias, primary hyperoxaluria, gout, and others.

This book is a remarkable achievement and will doubtlessly play an important part in student and postgraduate teaching. It will also be the first comprehensive reference book for the research worker—although here the number of references, generous as they are, will not be sufficient. Thus the only reference to the exciting story of thalassaemia—beginning some 30 years ago in Greece and Italy, then moving to the U.S.A. and back again to Europe, the first accounts of two types, the gradual recognition of their relation to the heterozygous and homozygous states—is a worthy article published by Montaleuti, Silvestroni, and colleagues in 1952. This, however, must not be taken as a criticism but as an indication to the prospective reader. A comprehensive collection of references on the haemophilias, for example, could fill a small book.

The book is well produced. With 69 illustrations and a detailed index the price of 37s. 6d. is very modest and well within the reach of the wide public this book deserves and will assuredly get. Only because one expects perfection from the Cambridge University Press is it pointed out that to write mg. (milligrams) at the beginning of a legend as Mg suggests magnesium to the biochemist. The name of the distinguished Athenian paediatrician Choremis is persistently misspelt, and at one time one had the impression that Continental names are anglicized as a matter of principle: Horlein, Schonheimer, Waldenstrom. This cannot be so, however, because Debré is given his accent and the discoverer of phenylketonuria, Fölling, is on occasion awarded his rightful diaeresis.

H. Lehmann.

FACIAL PALSY

Peripheral Facial Palsy: Pathology and Surgery. By Karsten Kettel, M.D. Foreword by Terence Cawthorne. F.R.C.S. (Pp. 341; illustrated. £6.) Oxford: Blackwell Scientific Publications. 1959.

Inspired by Terence Cawthorne, who writes an elegant foreword, Dr. Karsten Kettel has given us in monograph form the fruits of his unique experience of cases of facial palsy. Much of the text is devoted to the surgical alleviation of Bell's palsy and in particular to the indications for operative intervention. These latter are empirical and clinical, rather than electro-physiological. The author seriously contemplates surgery in cases where no signs of recovery are to be seen after two months; in acute cases with severe pain behind the ear; and in delayed cases where the spontaneous improvement is very inadequate and the galvanic response is strongly positive. In relapsing cases of facial palsy decompression should be performed as soon as possible. Regarding the problem of the aetiology of Bell's palsy, Kettel does not mention virus infection, but favours the hypothesis of Worms and Chams. Kettel believes that in facial palsy there is a combination of both primary and secondary ischaemia, due to a dysregulatio of the vasa nervorum. The author also deals in a cautious fashion with the question of surgery in cases of peripheral clonic facial spasm. There is an interesting account of Melkerson's syndrome, of familial bilateral relapsing facial palsy, angioneurotic facial oedema, and lingua plicata. Here the indications for surgery are as in cases of Bell's palsy.

Neurologists and otologists will both find Kettel's monograph useful and well illustrated, and the unusually fine bibliography is of particular value.

Macdonald Critchley.

INTERNATIONAL MEDICAL RESEARCH

World Medical Research. Principles and Practices. By Harry Sutherland Gear, M.D., D.P.H., D.T.M.&H., B.Sc., F.S.S. (Pp. 117+xii+5. 30s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

Dr. H. S. Gear, formerly an assistant director-general of the World Health Organization, has done a most useful service in giving us a bird's-eye view of the achievements, advantages, and limitations of international medical research, particularly as fostered by W.H.O. and other international agencies like F.A.O. and Unesco. He looks back first at the beginnings of medical research in ancient Greece and Rome, and then takes us through the Renaissance to the modern technological age. As examples of internationally sponsored projects he supplies thumb-nail sketches of progress in the eradication of malaria, the control of tuberculosis, the epidemiology of poliomyelitis, the problems of insecticide resistance, co-operative programmes towards better nutrition, and so on.

Perhaps the best chapters are those dealing with the difficulties and future of organized research by teams supported by international funds, for Dr. Gear recognizes the need for freedom for the individual researcher with real originality. It is here that the universities have the most important role to play, and the international agencies might give more encouragement and support to the foundation of new universities in the developing countries.

ROBERT CRUICKSHANK.

SEEING IN THE DARK

Night Vision. By Gaetan E. Jayle, Albert G. Ourgaud, L. F. Baisinger, M.D., and William John Holmes, M.D. Introduction by Sir Stewart Duke-Elder. (Pp. 408+xiv; illustrated. £5 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

In 1950 there was published under the auspices of the French Ophthalmological Society a quite outstanding monograph on *Night Vision and its Derangements*, its main authors being G. E. Jayle and A. G. Ourgaud. The work under review is an abridged version of this monograph translated by L. F. Baisinger and W. J. Holmes and brought up to date by reference to papers published since 1950. Possession of the earlier book invites comparison, and it must be said that, apart of course from its being written in English, the new is eminently less readable and less interesting than the old. This is perhaps inevitable, since, allowing for new matter, it is of considerably less than half the length, with the aesthetic disadvantages of any synopsis. A further disadvantage is that, apart from a few textbooks and monographs, authors quoted in the text in relation to work before 1950 are not given in the list of references; for these the reader is referred to the original work.

This is not to deny the value of the new publication to the research worker, to those interested in the practical problems of vision at dim illumination, or to the clinician interested in the effects of ocular or systemic disease on mesopic or scotopic vision. In compared passages all the essential information and important references of the earlier work are given in the new, and one need do no more to emphasize the value of the translation than recall the acclaim so rightly accorded to the original monograph.

Of the additions perhaps the most interesting are in chapter 9, in which is reviewed much new work in relation to the lighting of roads, cars, aeroplane cockpits and landing-grounds, mines, and railways, and in which mention is made of the possible value of infra-red radiation in solving still existing problems.

To those who read French literature but slowly and wish to keep right up to date this work will be valuable; but more interesting, and for referring to original work of the past even more essential, will be Jayle and Ourgaud's original monograph.

A. J. B. GOLDSMITH.

AN ANCIENT DISEASE

Gouty Arthritis and Gout. An Ancient Disease with Modern Interest. By Thomas E. Weiss, M.D., F.A.C.P., and Albert Segaloff, M.D., F.A.C.P. (Pp. 221+xii; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Gout as a disease entity with clearly defined clinical, biochemical, and pathological criteria represents an ideal subject for a monograph such as this, which has as its object the "compilation of theories, facts, clinical observations, pathology, treatment and extensive bibliography." The authors have indeed covered the field very thoroughly. Nearly 400 references, clearly documented, provide at the least a valuable bibliography, though the transatlantic habit of referring to these by numbers in the text instead of using the names of the authors makes for the recurring necessity of turning to the references at the end, thus interrupting consecutive reading.

One has the impression throughout that the authors are inclined to bow to the opinions of others rather easily, sometimes perhaps a little uncritically, so that the reader is often left in doubt as to the relative value of different hypotheses or of one regime of treatment versus another. They do, however, go so far as to state, very properly, that cinchophen no longer has a place in the treatment of gout. They discuss high-dose salicylate administration as if it were practical therapy. Surely very few patients to-day would accept a lifetime intake of 90 grains or so of aspirin a day.

Perhaps the only valid criticism is that the book is written, as the authors state, for "the student, clinician and investigator" each of whom must surely require information at a different level, and it must be almost, if not quite, impossible to present material of this nature in a form ideally suited to each. Apart from this they give a clear account of the modern approach to this ancient disease. The book is well illustrated and very clearly printed and would represent a most useful addition to any hospital library.

R. M. MASON.

A DOCTOR IN MANY LANDS

Microbes, Men, and Monarchs: A Doctor's Life in Many Lands. By Aldo Castellani, M.D., F.R.C.P. (Pp. 287; illustrated. 25s.) London: Victor Gollancz, Ltd. 1960. (Also published without illustrations by Doubleday and Company Inc., Garden City, New York, under the title *A Doctor in Many Lands.*)

This autobiography traces the life and adventures of one of the most flamboyant figures in tropical medicine, whose experiences have ranged from sleeping-sickness in Uganda to yaws in Ceylon, from the Senate of Rome to a busy practice in Harley Street, and whose discoveries have shed light on the subject throughout this century.

Castellani's life could hardly have avoided being unordinary when one considers (*a*) his ancestry—which included a saint on one side and Florentine aristocrats on the other, (*b*) his training—which in his particular field was inspired by Manson himself, and (*c*) his environment—which necessitated close association with some of the most infamous (for example, Mussolini) and most famous (for example, Marconi and Paderewsky) figures of our age. His immense vitality had full scope when, at one and the same time, he was lecturer in mycology at the London School of Tropical Medicine,

the professor of tropical medicine at the Louisiana State University in New Orleans, and the occupant of a chair in the University of Rome.

The autobiography vividly illustrates his three major passions: the foremost is his interest in research, which early in his life led to the establishment of his reputation by the discovery of trypanosomes in the cerebrospinal fluid of cases of sleeping-sickness, and which to-day, at the age of over 80, impels him to maintain and study cultures of pathogenic fungi in his laboratory in Lisbon; the second passion shows him in the role of court physician, a survivor of a past age when men of our profession were not infrequently in the inner councils of their king; the third passion of his life is anglophilia, which began when he was a boy in Florence and easily survived the last war—hardly surprising when one remembers the numerous patients, colleagues, and relations he has accumulated in this country. They and many others will read this book with interest and pleasure.

P. C. C. GARNHAM.

BIOCHEMISTRY OF BLOOD

Biochemistry of Blood in Health and Disease. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. (Pp. 543+ix; illustrated. £6 6s.) Oxford: Blackwell Scientific Publications. 1959.

This book deals with the blood and its chemical, humoral, and cellular constituents. It has been inspired by our increased ability to measure these constituents as the result of developments in biochemistry, chromatography, electrophoresis, radioisotopes, and the large-scale manufacture of many new types of analytical apparatus.

Part I deals with the blood as a medium for the transport of proteins, nitrogen compounds, carbohydrates, and lipids. Part II is about blood as part of the regulatory system whereby water, electrolytes, vitamins, enzymes, hormones, and other substances involved in the maintenance of the relatively constant internal milieu are appropriately controlled. Part III discusses the blood, and in particular its cellular constituents, as a defence system against injury, shock, and infection. These are large topics to deal with, as it were, through the agency of a blood sample.

Just as one may get new pictures by shaking a kaleidoscope, so a rearrangement of familiar material or concepts may give new insights into the processes of disease; but though the book is clearly written it is doubtful whether Dr. Kugelmass has really succeeded in this aim. For example, his chapter "Blood as a Carrier of Tissue Minerals" tells us a certain amount about the distribution of sodium, potassium, and chloride in different compartments of the body and their movement between these compartments, but one is much more interested in the regulation of these substances by the kidneys and the adrenals than their carriage in the blood. There is, in other words, a great deal of information in this book, but one cannot see any obvious advantages in having collected it in this way. Moreover, it is almost certainly far too large a subject to be handled by a single author. The references at the end of each chapter are at first sight impressive, but too small a proportion come from the last five years. Modern views on the relation between direct and indirect bilirubin and on the inborn errors of bilirubin metabolism do not appear to have been noticed. The book is well produced, with a good index, and is printed on a large page in double column.

L. J. WITTS.

ECOLOGY OF PESTS

Consequences of Disturbance. The Pest Situation Examined. By Alan Mozley, D.Sc., Ph.D., F.R.S.E. (Pp. 61+x. 9s.) London: H. K. Lewis and Co., Ltd. 1960.

This short monograph extends the series by Dr. Mozley expounding his ecological approach to the study and control of pests, particularly the molluscan pests conveying fluke infections to man and animals. He contends that after natural or man-made disturbance of the environment organisms with limited tolerance are eliminated, and in the absence of competition the growth of opportunist species is unrestricted and they tend to become pests. The schistosome vectors exemplify this, being scanty in undisturbed, uninhabited country, but very numerous in collections of artificial water such as dams and irrigation canals.

One of the important tasks of this age is to reduce the enormous losses caused by pests. A problem of this nature is generally exceedingly complex, and judgment and discrimination are required in selecting control measures. The author deprecates reliance on strong insecticides or molluscicides alone and advocates biological and ecological methods of controlling expansion of the pest population. It is known, for example, that some strains of snails resist schistosome infection which enfeebles susceptible strains; in a mixed community natural selection would favour the resistant strain. The author suggests using genetic measures such as this, or modifying the environment to the detriment of the pest species. He makes a plea for the encouragement of individual investigators rather than unwieldy teams, and he stresses the need for basic research, particularly into the ecology of pest communities instead of the study of individual species and environmental factors.

The author uses ecological terms which are often incomprehensible to the ordinary biologist. The book presents theses for the consideration of the research worker rather than advice to the field hygienist, who will not find it of practical value though the point of view may interest him.

T. H. DAVEY.

HUMAN PATHOLOGY

Principles of Human Pathology. By Edward B. Smith, M.D., Parker R. Beamer, Ph.D., M.D. Frank Vellios, M.D., and Dale M. Schulz, M.S., M.D. (Pp. 1,123+xi; illustrated. 95s.) New York and London: Oxford University Press. 1959.

The authors have arranged the contents of this new book so that the student is introduced to the general disturbances of function and structure in the first few chapters, and these are the best chapters in the book. That on the disturbances and regulation of blood sugar is an excellent example of what can be done in this respect. In the later chapters, where the diseases of the various systems are described, there does not seem to be the same new approach that is indicated in the more general sections, and the student will find it difficult to accept certain bald statements which are not supported by discussion. There is the inevitable difference in stress between subjects—for example, forensic pathology is dealt with in eight pages, and is altogether too condensed to be of much value, whereas rheumatic fever alone occupies seven pages and is adequate. The chapter on diseases due to the inhalation of dust is better, and does provide the student with the varying theories of causation which are at present under discussion. One of the best sections of the second half of the book is devoted to the kidney, and here the

physiology and physiopathology are well presented. Furthermore, the histological changes in the kidney are well demonstrated in an excellent series of photographs, but this of course takes up 31 pages, and does represent the sort of elaboration which is required to tackle any one system.

One major criticism, which it is hoped will be removed in the next edition, relates to the photographs and photomicrographs. These should be investigated very carefully. Some of them are excellent, but others are worse than useless. The magnifications of the photomicrographs are nowhere included, and, as the plates range from half a page to a tiny corner of a page, it is difficult for the student to know what the lesion really represents. One of the worst pictures can be seen on page 804, where a chronic ulcer of the stomach is very badly represented. On page 578 there is a so-called "erythrophagocytosis" which is a series of meaningless smudges and should be replaced. Other very poor examples occur on page 626, "infarct of placenta," and page 763, "gross specimen of lung representing bronchopneumonia." As opposed to these, on page 691 the "healed infarct of myocardium" shows the standard which should be achieved. Finally, the photographs are not identified by numbers, so that they cannot be referred to in the text. Where the photographs are immediately adjacent to the text which they illustrate this is easy, but where no reference at all can be found to the photograph it is difficult for the student to understand the purpose of the illustration. As an example of this, on page 824, "follicular enterocolitis" does not appear to be described in the text. On page 1045, osteopetrosis is described as "a condition in which the sclerotics are blue." The whole volume is adequate but not up to the highest American standards.

A. G. Signy.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A Student's Guide to Obstetrics and Gynaecology. By Christopher J. Dewhurst, M.B., F.R.C.S.Ed., M.R.C.O.G. (Pp. 230; illustrated. 16s.) London: Cassell. 1960.

Transport and Accumulation in Biological Systems. By E. J. Harris, Ph.D., D.I.C., D.Sc. Second edition. (Pp. 279+xi; illustrated. 50s.) London: Butterworths Scientific Publications. 1960.

Somatosensory Changes after Penetrating Brain Wounds in Man. By Josephine Semmes, Sidney Weinstein, Lila Ghent, and Hans-Lukas Teuber. (Pp. 91+xiii; illustrated. 32s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960.

The Biology of Myelin. Edited by Saul R. Korey, M.D., with 51 participants. (Pp. 405+xxii; illustrated. 70s.) London: Cassell.

Holocaust! By Paul Benzaquin. (Pp. 256; illustrated. 21s.) London: Frederick Muller, Ltd. 1960.

Reading Disability. A Medical Study of Word-Blindness and Related Handicaps. By Knud Hermann, M.D. (Pp. 183. Dan. Kr. 22.) Copenhagen: Ejnar Munksgaard. 1960.

Klinische Chirurgie für die Praxis. Vol. I, Part 3. Edited by Dr. O. Diebold, Dr. H. Junghanns, and Dr. L. Zukschwerdt. (Pp. 618; illustrated. DM. 54.) Stuttgart: Georg Thieme Verlag. 1960.

Oxymetrie. Theorie und Klinische Anwendung. Edited by Kurt Kramer. (Pp. 206+vi; illustrated. DM. 39.60.) Stuttgart: Georg Thieme Verlag. 1960.

Fundamental Aspects of Normal and Malignant Growth. Edited by Wiktor W. Nowinski. (Pp. 1,025+xv; illustrated. £10 10s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

Marriage and Periodic Abstinence. By J. G. H. Holt, M.D. (Pp. 86+x; 10s. 6d.) London: Longmans. 1960.

Chance, Skill, and Luck. The Psychology of Guessing and Gambling. By John Cohen. (Pp. 201. 3s. 6d.) London: Penguin Books, Ltd. 1960.

Klinische Physiologie: Aktuelle Probleme in Übersichten. Vol. I, Part 2. Edited by Dr. W. A. Muller. (Pp. 203; illustrated. DM. 15.30.) Stuttgart: Georg Thieme Verlag. 1960.

Clinical Medicine, the Modern Approach. By A. E. Clark-Kennedy, M.A., M.D.(Cantab.), F.R.C.P.(London), and C. W. Bartley, M.A., D.M.(Oxon.), M.D.(McGill), M.R.C.P.(London). (Pp. 425+x. 25s.) London: Pitman Medical Publishing Co., Ltd. 1960.

Anatomy and Physiology for Radiographers. By J. E. Blewett, M.D., D.M.R., F.F.R., and A. M. Rackow, B.Sc., M.B., D.M.R.E. (Pp. 322+viii; illustrated. 37s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Individuum und Krankheit. Grundzüge einer Individualpathologie. By Friedrich Curtius. (Pp. 467; illustrated. DM. 88.) Berlin, Göttingen, Heidelberg: Springer-Verlag. 1960.

Anaerobic Bacteriology in Clinical Medicine. By A. Trevor Willis, Ph.D.(Leeds), M.B., B.S.(Melb.). (Pp. 163+xii; illustrated. 30s.) London: Butterworth and Co. (Publishers) Ltd. 1960.

A Textbook of Surgical Pathology. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.(Ed.), F.R.F.P.S.(Glas.), Hon.F.A.C.S., Hon.F.R.C.S.(Eng.), and Bruce M. Dick, M.B., F.R.C.S.(Ed.), F.R.F.P.S.(Glas.). (Pp. 704+viii; illustrated. 75s.) London: J. and A. Churchill Ltd. 1960.

Medical Physiology and Biophysics. Edited by Theodore C. Ruch, Ph.D., and John F. Fulton, M.D. Eighteenth edition of Howell's *Textbook of Physiology*. (Pp. 1,232+xxii; illustrated. £5 12s.) Philadelphia and London: W. B. Saunders Company. 1960.

The Child with Mongolism (Congenital Acromicria). By Clemens E. Benda, M.D. (Pp. 276+xvi; illustrated. $9.50.) New York and London: Grune and Stratton. 1960.

Irrwege der Menschlichen Gesellschaft. Medizinisch-psychologische Kritik Sozialer Unzulänglichkeiten. By Dr. Julius Bauer. (Pp. 151. Sw. fr. 18.50.) Liestal: Verlag Ars Medici Lüdin AG. 1959.

Manual of Histologic and Special Staining Technics. Armed Forces Institute of Pathology. Second edition. (Pp. 207+ix. 43s.) New York, Toronto, London: Blakiston Division, McGraw-Hill. 1960.

Social Rehabilitation of the Subnormal. By Herbert C. Gunzburg, M.A., Ph.D.(Vienna), F.B.Ps.S. (Pp. 282; illustrated. 27s. 6d.) London: Baillière, Tindall and Cox. 1960.

The Cell Nucleus. Proceedings of an Informal Meeting held by the Faraday Society, August 31-September 1, 1959. Chairman: Professor J. S. Mitchell, F.R.S. (Pp. 269+xiii; illustrated. 50s.) London, Toronto, Sydney, Wellington, Durban: Butterworths. 1960.

Board and Table Games from Many Civilizations. By R. C. Bell, M.B., F.R.C.S. (Pp. 208+xxiv; illustrated. 21s.) London, New York, Toronto: Oxford University Press. 1960.

The Edge of Objectivity. An Essay in the History of Scientific Ideas. By Charles Coulston Gillispie. (Pp. 562+vii; illustrated. 42s.) Princeton, N.J.: Princeton University Press. London: Oxford University Press. 1960.

The Symposium on Thyro-Gonad-Adrenal-Pituitary Relationships. Proceedings held at New Delhi, October 2-4, 1959. (Pp. 131+xi; illustrated. R.10.62.) New Delhi: National Institute of Sciences of India. 1960.

V Congreso Venezolano de Cirugia (Relatos Oficiales y Correlatos). Secretaría de la Sociedad Venezolana de Cirurgia. (Pp. 504; illustrated.) 1960.

Medicina Neotropical. Esquistosomiasis Mansonica. (Pp. 232; illustrated.) Caracas: Laboratorio Behrens. 1960.

A Question of Surgery. By Michael Fitzwilliam. (Pp. 208. 15s.) London: Jarrolds. 1960.

Practical Clinical Management of Electrolyte Disorders. By William J. Grace. (Pp. 132+xi.) New York: Appleton-Century-Crofts, Inc. 1960.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 22 1960

HEALTH SERVICES IN THE FEDERATION OF RHODESIA AND NYASALAND

The Monckton Commission, the report[1] of which was published last week, has studied both the practical structure of the Federation of Rhodesia and Nyasaland and also the allocation of functions between the Federal and Territorial Governments. Its recommendations on the first have at least been clear and secured overwhelming support among members of the Commission, but its review of functions lacks both clarity and general agreement. One of the most important Federal functions, after service of the Public Debt, is Health, which ranks financially with Education, and accounts for 12½% of its total expenditure and 34% of its staff roll. It is, moreover, the principal means by which the results of federation are brought home to the average citizen. The Commission found considerable opposition to the Federation in itself, and considered that if the federal association is to survive radical reforms are necessary and that there should be a substantial transfer of functions from the Federal to the Territorial Governments. The first principle guiding the reallocation should be that matters affecting the day-to-day life of the inhabitants should be Territorial subjects, and on this basis it has recommended that health services should again become Territorial, with the exception of major public health schemes, control of poisons and drugs, and international aspects of health control. It concludes with an enigmatic paragraph reading:

> "But in order not entirely to sacrifice the advantages to be gained from a health service with uniform standards, uniform conditions of service and liability to transfer within the whole of the Federal area, we recommend that the Territorial Governments with, or without, the assistance of the Federal Government, should negotiate the setting up of a Central African Health Service, possibly in the form of a statutory commission or corporation to achieve the advantages stated."

These proposals have such notable implications for the efficient working of the services and for the welfare of the people that they deserve careful examination.

The history, development, and difficulties of the medical services in Rhodesia and Nyasaland have recently been admirably surveyed in this *Journal* by Dr. H. S. Gear.[2] When the Federation was first formed in 1953 health services were put in the "Concurrent Legislative List" of matters on which both Federal and Territorial Governments might legislate, but the Federal Government very soon, by an administrative act, brought practically all of them under a Federal Ministry of Health, perhaps in order to ensure that the poorest of the Territories, Nyasaland, could draw freely from the Federal pool. The structure set up included a Federal Minister and Secretary for Health, with a Federal Advisory Board of Health and three Territorial Directors of Medical Services, responsible to the Federal Ministry. Certainly in some ways this system worked well, and the gap between medical facilities in the three Territories was narrowed, though not closed. Medical expenditure in Nyasaland trebled in the first five years of the Federation, while that in Southern Rhodesia increased by only 45%. The system has received praise, but has not escaped criticism on the grounds that the Ministry exercises an over-centralized and bureaucratic control entirely foreign to a democratic community and is out of touch with the detail of medical needs. A Commission of Inquiry was set up two years ago to advise on health and medical services in the Federation, though it was really confined by its terms of reference to the administration of Federal Government hospitals and the provision of specialist services. The report[3] of this Commission drew attention to the unusual, perhaps unique, federal structure for health services, for it is the general practice in Federations elsewhere and even in unitary Governments to devolve these services to territorial, provincial, or regional authorities. However, the Commission of Inquiry was impressed by the advantages which had been gained, rejected suggestions for reversion to a territorial system, and considered that the Federal Government's assumption of responsibility for practically all health matters had been justified. It found, however, that the service was, to some extent, over-centralized and recommended a revision of the Federal Advisory Board of Health and the establishment of territorial regional advisory health boards and local hospital advisory committees to ensure contact of the Ministry with local needs.

The constitution of the Federation which led to the Federal Health Services was laid down after local consultation by the British Government, and includes

[1] *Report of the Advisory Commission on the Review of the Constitution of Rhodesia and Nyasaland*, 1960, H.M.S.O., London. Price 8s. net.
[2] Gear, H. S., *Brit. med. J.*, 1960, 2, 525.
[3] Federation of Rhodesia and Nyasaland. *Report of the Commission of Inquiry into the Health and Medical Services of the Federation, 1959*, 1960, Salisbury, Southern Rhodesia.
[4] See *Brit. med. J.*, 1959, 1, 1024, and 1960, 2, 206.

a clause requiring its review at some time between 1960 and 1963. The Monckton Commission was set up to advise on the constitution programme and framework as a preliminary to this review. One aspect of its political recommendations is now common knowledge, and the controversy over it has distracted attention from other important parts. The principal subjects to be reallocated from the Federal to the Territorial Governments are Health, Education, Agriculture, and Roads. The largest of these is Health, but the recommendations on this subject show marked evidence of conflict of thought between members of the Commission. Vacillation appears in the paragraph quoted above, and a dissentient note by some members of the Commission pertinently asks in what way this proposal differs from an effort to reform the Federal Service and what advantage is to be gained if decentralization is to be practised and immediately reversed. The internal conflict is revealed by the number of dissentients; the majority Report is signed by 22 persons, of whom 9 dissented from this recommendation. This is in itself a significant indication of doubt about the wisdom of the proposals, but the significance is increased by the pattern of dissent. All but one of the members from outside the Federation supported the recommendation. Eight of the 11 from within the Federation dissented from it. It looks very much as if those who knew the previous system and know the present one prefer the latter. The basic principle accepted by all has been rejected in practice by a considerable minority. The administration of services affecting the day-to-day life of the inhabitants should be under a large measure of local control, but perhaps some of the advantages of decentralization might have been gained by adoption of some version of the Commission of Inquiry's recommendations, or by the creation of a National Health Service administered by a Statutory Commission, ensuring the maintenance of existing employer/employee relationships and the provision of finance from all four Governments, as is recommended by three of the dissentients.

Confusion of objective is now inevitable, and the sooner the resultant uncertainties are resolved the better for all concerned—patients, present staff, and potential recruits. The last group is particularly important at the moment because publication of the report coincides with a drive for medical recruits which was planned before the Commission framed its report. The appeal is based on the quality of the job to be done, the scope it gives for professional capacity and initiative, and the service which doctors can render to communities thirsty for medical help. These claims are just. They have, of course, another side, for appointment may entail living in relatively small communities, distant from specialist medical colleagues. This isolation is fast diminishing. Salisbury is now a university town and hopes soon to have a medical school.[4] It already has fine hospitals where standards of specialist and general services are high, and Bulawayo, Lusaka, Kitwe, Zomba, and Blantyre, follow in its path. The careers which are offered have real advantages for those who are professionally and personally self-reliant and wish for a wide range of professional responsibility. The confusion which the Report of the Monckton Commission will inevitably cause needs quick clearance to ensure the progress of present medical development, the contentment of the present staff, and to satisfy potential recruits that a settled career is open to them.

BUERGER'S DISEASE

Does Buerger's disease (thromboangiitis obliterans) exist as a specific disease entity? Since Buerger's original description of the condition in 1908[1] the syndrome of inflammatory peripheral vascular occlusions affecting not only the leg vessels but also those of the cerebral, coronary, and other circulations has figured prominently in both medical textbooks and medical teaching. It is only of recent years that the specific nature of the disease has been called into question. C. M. Fisher,[2] in an excellent critical review of the literature, seriously questioned the specificity of both the clinical and pathological features of the syndrome, although he was primarily concerned with the cerebral aspects of the disease. I. Gore and S. Burrows[3] have also joined the group of nosological doubters. The subject has again been reopened by the assembly of powerful evidence in support of these authors by S. Wessler and colleagues.[4]

On what evidence did Buerger base his claims? In his first paper on the subject in 1908 he reported on the vascular pathology of 11 extremities amputated because of gangrene. At this time he did not consider the disease to be inflammatory in nature but to be due primarily to unexplained arterial thromboses. However, in 1914 he radically modified this concept when he published his observations that superficial phlebitis often accompanied the arterial occlusions.[5] In two of the 11 cases described in

[1] Buerger, L., *Amer. J. med. Sci.*, 1908, **136**, 567.
[2] Fisher, C. M., *Medicine*, 1957, **36**, 169.
[3] Gore, I., and Burrows, S., *Amer. J. clin. Path.*, 1958, **29**, 319.
[4] Wessler, S., Ming, S., Gurewich, V., and Freiman, D. G., *New Engl. J. Med.*, 1960, **262**, 1149.
[5] Buerger, L., *J. med. Res.*, 1914–15, **31**, 181.
[6] —— *J. Int. Chir.*, 1939, **4**, 399.

Buerger's first paper[1] the deep arteries and veins had shown some of the features of acute inflammation, the occluding clot in these vessels resembling the intravascular clot found in the acutely inflamed superficial veins described in his second paper.[5] Buerger then assumed that the acute inflammation in the superficial veins reported in his second paper was the counterpart of the acute inflammatory process occurring in the arteries which he had observed in two instances in his original series in 1908. Of the 42 amputated legs studied by Buerger up to 1914 only the two in his original paper showed the acute arterial lesions that he had come to consider as the only absolute diagnostic criteria of the disease. He explained his failure to find the acute inflammatory lesion more often by assuming that the acute lesions had "burnt" themselves out by the time of amputation. Buerger's case is further weakened by the fact that even the "specific" acute arterial lesions he described so well are frequently encountered in other occlusive peripheral vascular lesions. In addition, the patients in many of the cases he studied had arterial occlusions that extended higher than the level of the amputation, so that the state of the arterial tree proximal to that level was largely unknown. A further major defect of his thesis was that necropsies on only three of his 42 cases were reported, and in each of these three cases arterial atherosclerosis was widespread and could have explained the peripheral arterial occlusions.

Finally, the precise clinical criteria of Buerger's disease have never been laid down. Although Buerger had originally stated that he observed the disease most frequently among male Jews in the third and fourth decades, in his paper in 1939[6] he avoided any clinical definition of its natural history or aetiology. In the light of this uncertainty of the exact pathology of thromboangiitis obliterans and the absence of any clinical definition of the syndrome, the analysis of Wessler and his colleagues[4] is a valuable contribution. They found that a clinical diagnosis of thromboangiitis obliterans could not be made with precision in any of the young Jewish males entering the Beth Israel Hospital in Boston during the past decade with peripheral vascular disease, a population that could on Buerger's original account be expected to yield a considerable number. Furthermore, a study of 35 leg-amputation specimens by these authors revealed no evidence in any instance of the acute arterial lesions described by Buerger and neither did a concurrent examination of 66 lower limbs amputated for atherosclerotic gangrene. The "specific" acute lesion of the superficial veins described by Buerger was observed fairly frequently in patients with a wide variety of thrombotic venous lesions, and also in many patients with arterial insufficiency due to atherosclerosis. The authors felt obliged to conclude that their observations provided no evidence for the clinical or pathological specificity of a disease which they find is indistinguishable from other causes of peripheral arterial occlusion.

As the aetiology is unknown, the clinical syndrome undefined, and the pathological features non-specific, it is not surprising that the weight of circumstantial evidence from this and other careful studies compels the conclusion that there is no such disease entity as Buerger's disease. However, a major contribution of Buerger's work has been the stimulus to the relatively neglected study of the pathology of peripheral vascular disease that his controversial observations have afforded.

IMMUNIZATION AGAINST WHOOPING-COUGH

Great changes have taken place in the incidence and severity of whooping-cough in the last five years. Notifications and deaths in 1958 were only about one-third as high as the averages of the previous three years, which in themselves had shown a marked reduction on those before 1955. The case fatality rate has also continued to decline during this period. Whooping-cough vaccines in use in this country are of known potency, and since it has been shown that their immunizing capacity can be estimated in the laboratory there is no longer any necessity for continued field trials. All but two of the local health authorities now provide whooping-cough vaccination, and over half a million children in England and Wales completed a primary course in 1959; there were fewer deaths (25) from the disease in 1959 than ever before. It would be surprising if this widespread use of vaccines of known immunizing power did not lead to a great reduction in incidence and mortality, and there can be little doubt that immunization can claim much of the credit for the favourable trend in the figures referred to above. The bare statistics do not tell the whole story. The reduction in incidence and severity have saved parents a lot of anxiety and loss of sleep.

When immunization results in the virtual elimination of a disease it is inevitable that some will question the continued need for routine inoculation of all infants. Parents to-day, seeing that the risk of contact with diphtheria is small, are prone to feel that there is little need for immunization against that disease, but outbreaks of diphtheria in different parts of the country during the last two years have shown how wrong this view is. Whooping-cough has not nearly

[1] Cockburn, W. C., reported in *Brit. med. J.*, 1959, 1, 1343.

reached the stage of virtual elimination seen in diphtheria, and to question the continued need for vaccination against this disease is surely premature. But altering circumstances call at least for a continuous scrutiny of preventive measures.

It has been known for some time that pertussis vaccination might be followed very rarely by encephalopathy. However rare such an event may be, it assumes proportionately more importance when incidence and mortality reach such low levels that the risk of death from whooping-cough itself appears remote. Where mortality from whooping-cough is high it may be that a very small risk in the prophylactic can be accepted. There is good reason to believe that if general immunization against pertussis was abandoned mortality would soon rise again. However, there is a continuing obligation on those responsible for immunization to ensure that in preventing disease they do as little harm as possible. The paper by Dr. Justus Ström in this issue (p. 1184) therefore calls for serious notice. In Sweden 36 cases of neurological sequelae of pertussis vaccination were described between 1955 and 1958. During this period 215,000 children were given the vaccine in the child-welfare clinics. Thus it appears that about one in 6,000 vaccinated children developed neurological complications. Most of the 36 were restored to health, but there were 4 deaths, and 9 cases of severe encephalopathy. The occurrence of complications after vaccination in Britain on the scale reported from Sweden, while the present low incidence of whooping-cough remains, would call for serious reconsideration of our attitude to pertussis vaccine. But the Swedish figures are far higher than anything reported in Britain. The most recent estimate put the frequency of neurological sequelae after the administration of British whooping-cough vaccines at less than one case in a million injections.[1] Nevertheless there must be some uneasiness until the reasons for the high complication rate reported from Sweden are known.

SALICYLATE POISONING

The basic principles in dealing with any ingested poison are to eliminate it and to counteract the mechanisms by which it endangers life. For only a few poisons is there an effective antidote. Salicylates, and particularly methyl salicylate (oil of wintergreen), can be retained in the stomach for several hours, and so gastric lavage is essential. The risks of inhalation of gastric contents if the patient is comatose must be avoided. It is well in all cases to empty the stomach with a Senoran's evacuator; if this cannot be done until late, the fluid should be tested with ferric chloride solution to see if salicylate is present. Washings should be similarly tested.

Absorbed salicylate is eliminated in the urine. It is not metabolized, but some is slowly conjugated with glycine and glycuronic acid. It is known that renal clearance of salicylate is increased if the urine is alkaline. This fact, and the presence of acidosis, forms the basis for the large doses of alkali formerly given. In the early stages of poisoning, however, "salicylate dyspnoea" causes a respiratory alkalosis. To gain the benefit of an alkaline urine without the disadvantage caused by large doses of alkali, R. C. Feuerstein and colleagues[1] facilitated the excretion of salicylate by making use of the prompt rise in *pH* of the urine which results from enhanced excretion of sodium and potassium caused by acetazolamide. The theoretical objection that acetazolamide, if given during the phase of metabolic acidosis, when most poisoned patients are seen, would worsen the acidosis was not experienced clinically. Sodium lactate was given parenterally to cover sodium losses. Caution is necessary in using acetazolamide, and the advantage of causing rapid excretion of salicylate must be weighed against the effects of upsetting the body's homoeostatic mechanisms. J. B. Rentsch and colleagues[2] suggest that a plasma salicylate level of 40 mg. per 100 ml. calls for other measures to reduce it, but admit that the decision must not be based on blood levels alone.

Which of the extrarenal methods of removing poison by dialysis may be employed must depend partly on which is available. The artificial kidney is probably best, and the disposable twin-coil machine can be moved to the patient if necessary. Failing this, exchange transfusion is advised. Peritoneal dialysis, while sound in theory, is unsatisfactory in practice, for fluid, while easy to put in, is sometimes difficult to remove.

How to deal with the effects of absorbed salicylate depends on a clear understanding of the effects they produce. These are hyperpyrexia, respiratory alkalosis, metabolic acidosis, dehydration, and ketosis. In therapeutic doses salicylates reduce temperature because, though they increase heat production, that is counteracted by increased heat loss through sweating. When the body water has been depleted by sweating, salicylate cannot cause further sweating, and hyperpyrexia results. It is more likely to occur in children than in adults, and a rectal temperature of 104° F. (40° C.) is an indication for sponging the body with cool water and alcohol. The initial respiratory alkalosis results from overbreathing caused by the direct stimulant action of salicylate. It is transient (six to eight hours) and not of great clinical importance, except that excess bicarbonate at this stage may cause severe tetany. But it predisposes to the metabolic acidosis which follows, because the fall of pCO_2 leads to decreased renal reabsorption of bicarbonate and an increased excretion of sodium and potassium bicarbonate. The effect of this is to lower the buffering capacity of extracellular and intracellular fluid and to hasten metabolic acidosis. This results from the salicylate radical itself, and also from the renal excretion of fixed base to combine with the organic acids which arise from altered carbohydrate metabolism.

[1] Feuerstein, R. C., Finberg, L., and Fleishman, E., *Pediatrics*, 1960, **25**, 215.
[2] Rentsch, J. B., Bradley, A., and Marsh, S. B., *A.M.A. J. Dis. Child.*, 1959, **98**, 778.
[3] Finberg, L., and Harrison, H. E., *Pediatrics*, 1955, **16**, 1.
[4] Weil, W. B., and Wallace, W. M., ibid., 1956, **17**, 171.
[5] Segar, W. E., and Holliday, M. A., *New Engl. J. Med.*, 1958, **259**, 1191.
[6] Campbell, E. J. M., and MacLaurin, R. E., *Brit. med. J.*, 1958, **1**, 503.
[7] Cohen, A. S., *New Engl. J. Med.*, 1956, **254**, 457.

In deciding how much alkali to give, pCO_2 estimations are not of great value, and blood *p*H values would be of more use. In the absence of laboratory control it is best to give bicarbonate in amounts sufficient to keep the urine alkaline to phenol red indicator—that is, to give a definite red colour (= *p*H 8.4). (Bicarbonate solution for intravenous use must not be boiled because this causes it to decompose. It must be sterilized by autoclaving and sealed under CO_2. In an emergency bicarbonate could be simply dissolved in sterile water.) Hyperventilation, sweating, and vomiting lead to dehydration, and this makes hyperpyrexia worse, so that the patient is in a vicious circle. As sweat is hypotonic, there is a greater loss of water than of electrolytes and hypernatraemia may result, particularly in infants.[3 4] Certain rare aspects of salicylate poisoning need to be borne in mind. Prolonged anuria may occur either from dehydration and shock[5] or from acute renal failure from tubular necrosis.[6]

The diagnosis of salicylate poisoning is seldom in doubt. The ferric chloride test is positive. But toxic doses of salicylates, by inhibiting enzyme systems and possibly by increasing production of adrenal corticosteroids, may cause glycosuria despite their opposing action of increasing "glucose demand." These findings in a dehydrated patient with hyperventilation may raise a suspicion of diabetic coma.[7]

NERVE ENDINGS IN MYASTHENIA GRAVIS

Myasthenia gravis is thought to be the result of a disturbance of transmission at the neuromuscular junction, but until recently histological examination has shown little abnormal in this disease apart from the changes found in the thymus. In 1905 Farquhar Buzzard[1] described aggregations of lymphocytes in the muscles which he called lymphorrhages. These are not a constant finding and may occur in other conditions such as thyrotoxicosis[2]; their significance is uncertain. In 1953 Dorothy Russell[3] described three types of abnormality in the muscles in this disease: the first was an acute change in which muscle fibres undergo necrosis, with resulting inflammatory reaction, and disappear; the second was a progressive atrophy of muscle fibres associated in the later stages with formation of lymphorrhages; and the third was a simple atrophy of single fibres or groups of fibres. She concluded that these changes were important in relation to the clinical evidence of muscle dysfunction but were not specific to myasthenia gravis and were not diagnostic of the disease.

A new technique for studying muscle biopsy specimens has been developed by C. Coërs.[4 5] It entails vital staining with methylene blue and the histochemical demonstration of choline esterase. E. R. Bickerstaff and A. L. Woolf[6] have studied seven cases of myasthenia gravis by this technique, and found abnormalities in the terminal end-plates of the nerves. In three patients the biopsy specimens were from muscles only slightly affected clinically, and in two of these the end-plates were remarkably elongated or multiple, indicating an increase in length of the synaptic area; in the third patient, a boy aged 8 with a short history of myasthenia, the changes were much slighter. In these three cases there were no pathological changes in the muscle fibres. In the remaining four cases, two of which showed muscles with severe and two with slight myasthenia, changes were found in the muscle fibres—lymphorrhages, variation in fibre size, and, in two, degenerative changes in the fibre. There was also disorganization of the pattern of terminal innervation as a result of a remarkable sprouting of the terminal axons after their emergence from the nerve bundle. Elongation of the end-plates was also seen, but this was often obscured by the disorganization of the terminal innervation. These latter changes may be found in other diseases such as dermatomyositis and carcinomatous neuropathy, and Bickerstaff and Woolf think that they may be related to degeneration of muscle fibres and "inflammatory" exudates. They consider that elongation of the end-plates and the tendency to form multiple endings is characteristic of myasthenia gravis, though it is apparently not always detected. Violet MacDermot[7] examined biopsy specimens from the deltoid in eight patients: in five there was no clinical weakness of the muscle and in three slight weakness, but in all the cases there was the characteristic myasthenic response to decamethonium and edrophonium ("tensilon"). Routine stains showed histological abnormalities to be slight or absent, but the methylene-blue technique showed abnormalities of the distal nerve fibres and the motor-end plates in all eight patients. The motor end-plates varied considerably in size and shape; abnormally large and complex end-plates were found in six cases and some abnormally small end-plates were also found in all cases. The other main abnormalities were in the distal nerve fibres, which had swellings and irregularities involving both the axons and the myelin sheaths. MacDermot considers that these abnormalities of the distal innervation pattern are characteristic of myasthenia gravis, but that there is not yet sufficient evidence to say they are specific to the disease.

These findings are of the greatest interest in showing that anatomical abnormality in the distal innervation is a probable basis for the disturbance of physiology in myasthenia gravis, and also in showing that the abnormality exists in muscles not clinically affected by the disease.

INSTITUTIONS FOR THE SUBNORMAL

There were some separate hospitals for mental defectives before 1913, such as the Royal Earlswood Asylum, but it was after the passing of the Mental Deficiency Act of that year that hospital authorities began to make a consistent effort to separate defectives from psychotics. The new Mental Health Act (1959)

[1] Buzzard, E. F., *Brain*, 1905, **28**, 438.
[2] Dudgeon, L. S., and Urquhart, A. L., ibid., 1926, **49**, 182.
[3] Russell, D. S., *J. Path. Bact.*, 1953, **65**, 279.
[4] Coërs, C., *Acta neurol. belg.*, 1953, **53**, 759.
[5] —— and Woolf, A. L., *The Innervation of Muscle*, 1959, Oxford.
[6] Bickerstaff, E. R., and Woolf, A. L., *Brain*, 1960, **83**, 10.
[7] MacDermot, V., ibid., 1960, **83**, 24.

tends somewhat to blur the distinction between them again, and it is desirable to review the need for hospitals for the subnormal. This branch of medicine, more than any other, has suffered from neglect. Accommodation has often consisted of unsatisfactory, ill-adapted, grossly overcrowded premises. In spite of the fine work done by many institutions, suitable staff has been difficult to obtain, financing has been niggardly, and a custodial atmosphere has prevailed. The policy of building the institutions in isolated areas tended to divorce defectives from the community, and the study of mental deficiency from other branches of medicine. The very large units institutionalized the patients and hindered rehabilitation, and the economic slump made employment of the feeble-minded difficult. Social workers were seldom appointed. Large numbers of potentially employable young people of feeble-minded or low intelligence were detained for many years.

The number of mental defectives accommodated in hospitals or under guardianship reached a peak in 1955, when it was 64,674, and has since declined somewhat to 63,577 in 1958. In addition, 60,144 were under statutory supervision in 1958. The number under guardianship has declined most in recent years, while there has been little change in the number of those accommodated in institutions. The new Act and the recommendations of the Royal Commission which led up to it provide for increased participation by the local authorities in caring for the mentally handicapped. In particular it is important that the children should not be denied privileges accorded to the normal child and that they should not be isolated from the community, which must be educated to tolerate them. While the provision of special training centres and, later, of hostels, should reduce the burden on the hospitals, there were meantime still 5,753 on the hospital waiting-lists in 1958 and overcrowding was officially estimated at 9.5%. The need for additional hospital accommodation, preferably in small units, is urgent, and it would be a mistake to close existing hospitals or wards, even when they are hardly suitable for their purpose, until the waiting-list can be accommodated.

There is a danger that special knowledge and training in the care of the mentally subnormal will be dissipated if it is too hastily assumed that the problem can be handed over to the paediatric unit, the general mental hospital, or the public-health authority without more ado. Existing hospital staff must play their full part in the new comprehensive service as it develops, and it would be unwise to encourage local authorities to build a completely separate service for the mentally handicapped. Hospital boards should not feel that the problem is no longer their concern, and they can help by actively planning a number of small residential nurseries in areas where the need is greatest, on the lines of the experiment recently described by J. Tizard.[1] When unsuitable buildings can be replaced by properly designed units, the maximum ward size should probably be of 20 beds. Links with the neighbouring university are worth fostering, and at least one unit might well be designated as a national centre for research into mental subnormality.

[1] Tizard, J., *Brit. med. J.*, 1960, 1, 1041.

PRESCRIBING SIMPLIFIED

The Joint Formulary Committee, representing the medical and pharmaceutical professions, was set up in 1946 to compile a standard prescriber's formulary. As a result of the admirable and unceasing labours of this committee, five editions of the *British National Formulary* have now been published, the fifth this year. In addition to the "standard" edition, which is issued to all general practitioners in the National Health Service, an "alternative" edition[1] is also prepared, and questions are sometimes asked about the difference between the two volumes. The difference is mainly a matter of approach. The standard edition starts with "Notes for Prescribers" in which the pharmacology and therapeutic application of a few important groups of drugs are briefly discussed. It then gives a list of preparations classified according to their predominant action on one of the body systems. The main part of the standard edition, however, consists of a formulary in which prescriptions are arranged on pharmaceutical principles —that is, all creams, injections, lotions, mixtures, tablets, and so on are collected and listed as separate groups. The formulary of the alternative edition, on the other hand, is based on the therapeutic approach. The preparations are classified according to their site of action, and each subdivision is headed by a short commentary in which the therapeutic indication and value of the main drugs of the group are discussed. The first subdivision of the formulary, for example, which deals with drugs acting on the alimentary system, begins with a discussion of the antacids in which the advantages and disadvantages of sodium bicarbonate, magnesium and calcium salts, magnesium trisilicate, aluminium hydroxide, and anticholinergic agents (atropine and its congeners) are outlined. A list of suitable prescriptions incorporating one or more of these drugs follows. This scheme is followed consistently. It has the advantage that, according to their intended use, preparations of the same drug may appear in several places. For instance, morphine is mentioned as a gastro-intestinal sedative as well as in the section on analgesics.

The prescriber is therefore likely to choose one or the other edition of the *National Formulary* according to the purpose he has in mind. If, for instance, he wishes to prescribe a mixture containing atropine, it will be easier to find a suitable prescription in the standard edition. If, on the other hand, he intends to write a prescription for the treatment of, say, motion sickness, but has not made up his mind which drug to prescribe and by which route to give it, the alternative edition has obvious advantages.

[1] *British National Formulary, 1960, Alternative Edition.* Obtainable from the British Medical Association. Price 8s. (or interleaved copies 12s. 6d.) net.

Clinicopathological Conference

A CASE OF PULMONARY HYPERTENSION

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with pulmonary hypertension who developed renal complications. He was transferred to Hammersmith Hospital in acute renal failure for treatment by the artificial kidney (Case No. 234,160; P.M. No. 9,020).

Clinical History

Dr. M. D. Milne: This patient was a male, aged 41 at death. He was quite well until 15 months before death. He then had a sudden feeling of faintness, and his own doctor diagnosed pleurisy. The next day there was severe pleuritic pain in the left chest, and three days later he had a haemoptysis. For the remainder of his life he suffered from recurrent haemoptysis, a little bright red blood being coughed up almost every day. He began to complain of exertional dyspnoea, which gradually increased in severity. There was never any orthopnoea or paroxysmal nocturnal dyspnoea. The blood-pressure was normal and a chest radiograph and bronchoscopy, performed at another hospital, were reported to be normal.

Six months before his death he developed severe diarrhoea, which persisted for two months and then cleared spontaneously. Sigmoidoscopy and barium enema examination were both normal. Three months before his death he had a particularly severe attack of left-sided pleurisy, and on examination he was found to show signs of right ventricular enlargement and pulmonary hypertension. A diagnosis of pulmonary arterial occlusion was made and he was treated with anticoagulants, "dindevan" (phenindione) being taken twice daily, and the dosage controlled by estimations of the prothrombin time. On examination at this time the systemic arterial blood-pressure was normal; there was increased jugular venous pressure with both an "a" and a "v" wave present, and there was a heaving right ventricular impulse. There was an accentuated pulmonary second sound, this being normally split. A high-pitched, blowing, systolic murmur was audible at the left sternal edge. The liver and spleen were just palpable, but there was no peripheral oedema. Chest radiograph showed gross enlargement of the pulmonary arteries, and the electrocardiograph was typical of right ventricular hypertrophy.

Acute Renal Failure

Two months after the start of anticoagulant therapy he developed a fever, a generalized erythematous rash, and enlargement of lymph glands. The haemoglobin and white cell count were normal, and the Paul–Bunnell reaction for glandular fever was negative. Four days later there was severe oliguria and he was uraemic, with a blood urea of 120 mg./100 ml. Blood cultures were negative, and there was no proteinuria. There was now a petechial element in the rash. After two days of oliguria he was drowsy and obviously very ill. He was almost completely anuric, and there was severe nausea with some vomiting. He was treated with "sulphatriad."

He was transferred to Hammersmith Hospital after five days of acute renal failure, as it was thought that treatment with the artificial kidney was now necessary. On admission he was drowsy but could be roused. The rash consisted of erythema, maculae, and a few petechiae. There was a heaving right ventricular pulsation and considerable increase of jugular venous pressure. There was a loud systolic murmur at the left sternal edge, and the liver and spleen were just palpable. The blood urea was 385 mg./100 ml., plasma potassium was 5.5 mEq/litre, and plasma bicarbonate 14 mEq/litre. The haemoglobin and total white cell count were still normal, but now there was an eosinophilia amounting to 28% of the total white cells. Because of the previous treatment with sulphonamides, cystoscopy and retrograde pyelography were carried out by Mr. R. Shackman, but no abnormality was found. The kidneys were obviously of normal size and shape. Four days after admission the blood urea had risen to 525 mg./100 ml., and plasma potassium to 7.0 mEq/litre. He was therefore treated by haemodialysis on the artificial kidney, and the blood urea fell to 145 mg./100 ml., and the plasma potassium to 6.0 mEq/litre. Two days after the dialysis a percutaneous renal biopsy was performed. This showed interstitial infiltration with plasma cells and damage of the proximal tubular cells. This showed that the renal lesion was reversible, provided he survived long enough for a diuresis to occur. A week later he was beginning to pass into an early diuretic stage, but the blood urea had risen to 435 mg./100 ml. A second haemodialysis was provisionally arranged for the following day, but was prevented by a severe and terminal relapse of the pulmonary disease. He suddenly complained of a severe pain over the sternum, and developed cyanosis with increase of the respiratory rate. The blood-pressure was normal but the electrocardiograph (Fig. 1) showed more severe abnormalities. In all leads there were tall, sharp P waves, depression of ST segments, and inversion of T waves. A diagnosis of a large pulmonary embolus was made. Despite all possible restorative measures, his condition deteriorated the next day. He was pale and restless and the blood-pressure had fallen to 80/60 mm. Hg. The blood urea had risen to 510 mg./100 ml., and he died in uraemic stupor about 24 hours after the last acute episode.

Clinical Diagnosis

(1) Acute oliguric renal failure, probably due to drug sensitivity, phenindione sensitivity being the most likely.

(2) Pulmonary artery occlusive disease with a terminal severe exacerbation.

(3) Pulmonary hypertension with right ventricular hypertrophy due to progressive pulmonary arterial occlusive disease, or to an unrecognized atrial septal defect.

Post-mortem Findings

Professor C. V. Harrison: The body was that of a man of average build, with a fading rash over the limbs and trunk and intravascular incisions in both groins.

Cardiovascular System.—The *heart* weighed 465 g. (normally 340 g.). The increase in weight was entirely

due to right-sided hypertrophy, the right ventricle measuring 7 mm. in the outflow tract (normally 2–3 mm.). Right ventricular hypertrophy was confirmed histologically and a few microscopic pyaemic foci were found. The tricuspid ring was dilated to a circumference of 150 mm. (normally 130 mm.). The pulmonary valve and artery were normal. The left side of the heart was normal. The aorta showed an occasional fatty plaque in the abdominal part but was otherwise healthy. The coronary arteries showed only minor atheroma. No thrombi could be demonstrated in the legs or pelvic veins.

Respiratory System.—The right pleura was totally obliterated by fibrous adhesions. The left pleura contained a few loose adhesions. The right lung weighed 1,250 g. (normally 450 g.), and the left lung 790 g. (normally 400 g.). The *right lung* showed some oedema, and in the middle lobe there was a large area, about 7 cm. across, riddled with small abscesses with consolidation between them. In the upper lobe there was an infarct, 2.5 cm. diameter, which proved to be infected and contained numerous streptococci. In the basal part of the lower lobe there was another infarct. *Left lung:* There were a few small infarct scars (Fig. 2) and some oedema. *Pulmonary arteries:* Pulmonary atheroma was not significantly increased. Down to a diameter of about 3 mm. the pulmonary arteries were free from emboli or other apparent disease. At about this level there were some emboli related to infarcts. In arteries below 3 mm. in diameter and down to about 300 μ microscopy revealed emboli of all ages, from recent to old scars, but there was no pulmonary arterial hypertrophy (Figs. 3 and 4). The most recent emboli were frequently infected by cocci (Fig. 5).

Alimentary System.—The intestinal tract was normal. *Liver* was enlarged, weight 1,990 g. (normally 1,550 g.), and the lobular markings were exaggerated. Histologically there was some centrilobular reticulin collapse suggesting past passive congestion. The *pancreas* showed fat necrosis in the immediately adjacent fat but no apparent lesion in the pancreatic tissue itself.

Genito-urinary System.—The *kidneys* together weighed 680 g. (normally 300 g.). Their surface was smooth. The cortex was wider than normal and appeared swollen. The markings were normal and there was no pigment in the medulla. There were a few tiny red points in the cortex, which on microscopy proved to be minute pyaemic abscesses. The renal vasculature was normal. There was a biopsy taken eight days before death and the post-mortem sections. There was little difference between them. The glomeruli were healthy. In the first and second convoluted tubules there was evidence of recent necrosis (Fig. 6) with regeneration (Fig. 7) which was now almost complete. There were casts in Henle's loops and a few casts in the collecting tubules. The interstitial tissue showed oedema and this appeared sufficient to account for the enlargement of the kidneys. The oedema fluid was infiltrated by plasma cells and some lymphocytes.

Other organs did not show any significant changes and were free from apparent disease on both macro- and microscopical examination.

Pathologist's Diagnosis

(1) Embolic pulmonary hypertension.
(2) Cor pulmonale with evidence of earlier congestive failure.
(3) Acute tubular necrosis apparently recovering.
(4) Uraemia.
(5) Streptococcal infection with septic pneumonic infection and abscess formation.

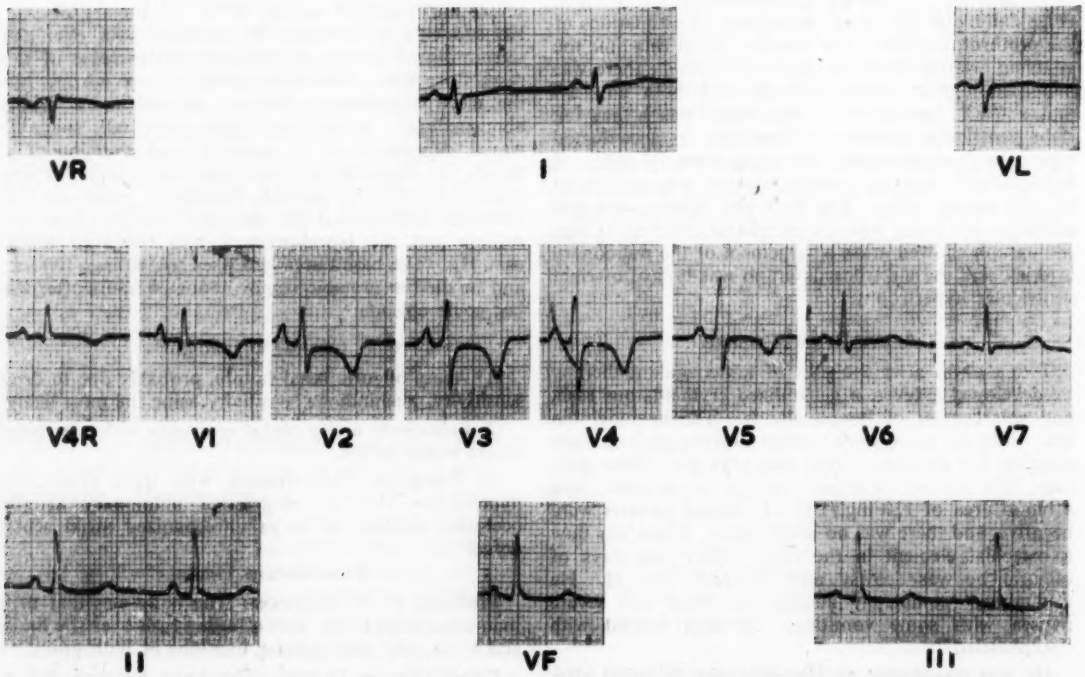


FIG. 1.—Electrocardiograph after terminal collapse, showing in all leads tall, sharp P waves, depression of ST segments, and inversion of T waves.

FIG. 2.—Healed pulmonary infarct. Alveolar walls are represented by black elastic tissue. The alveolar lumina are occupied by fibrous tissue. (Elastic/van Gieson stain. ×42.)

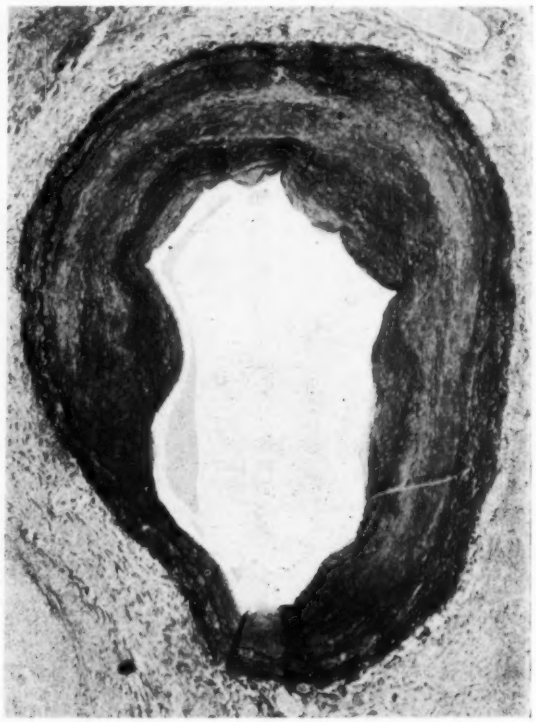


FIG. 3.—Pulmonary artery showing eccentric intimal thickening equal to five times the thickness of the media. The presence of elastic tissue in the intima implies that the thickening is old. (Elastic/van Gieson stain. ×34.)

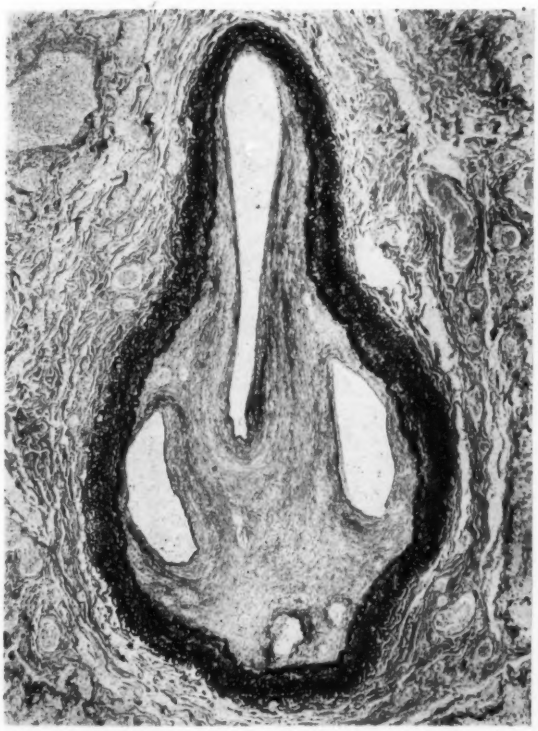


FIG. 4.—Pulmonary artery obliterated by fibrosis with three recanalizing channels. (Elastic/van Gieson stain. ×42.)

FIG. 5.—Pulmonary artery containing a more recent embolus with infection and abscess formation. (×42.)

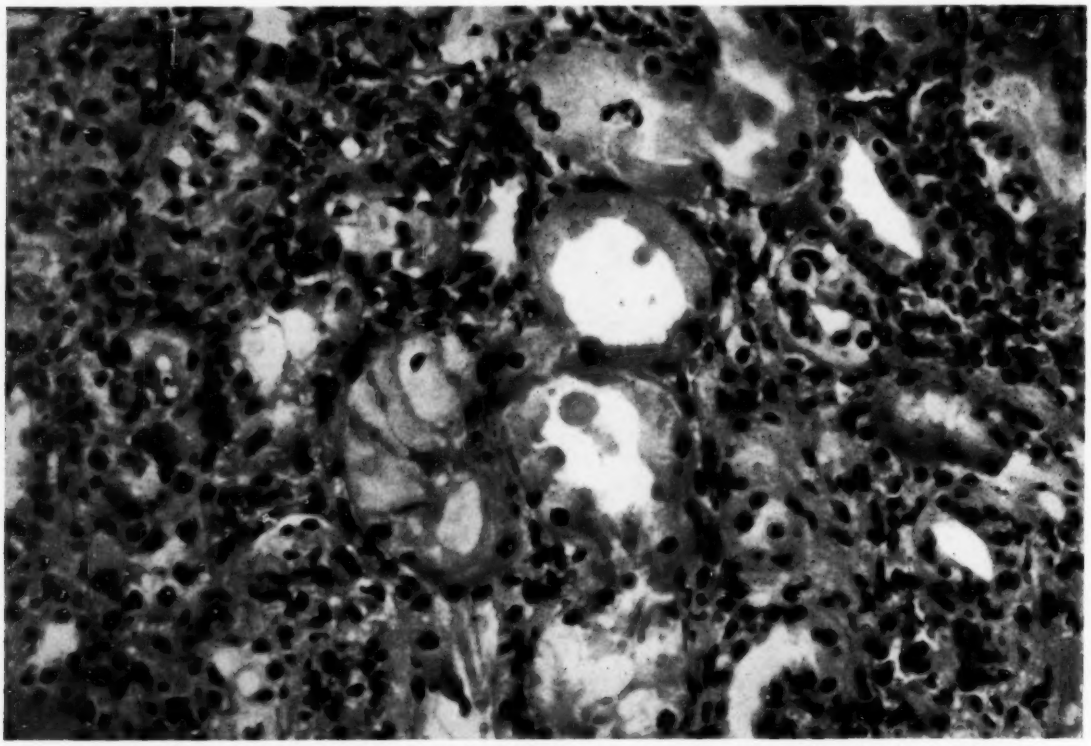


Fig. 6.—Kidney. Necrosis of proximal convoluted tubules. Note the swollen cells and loss of nuclei. (×399.)

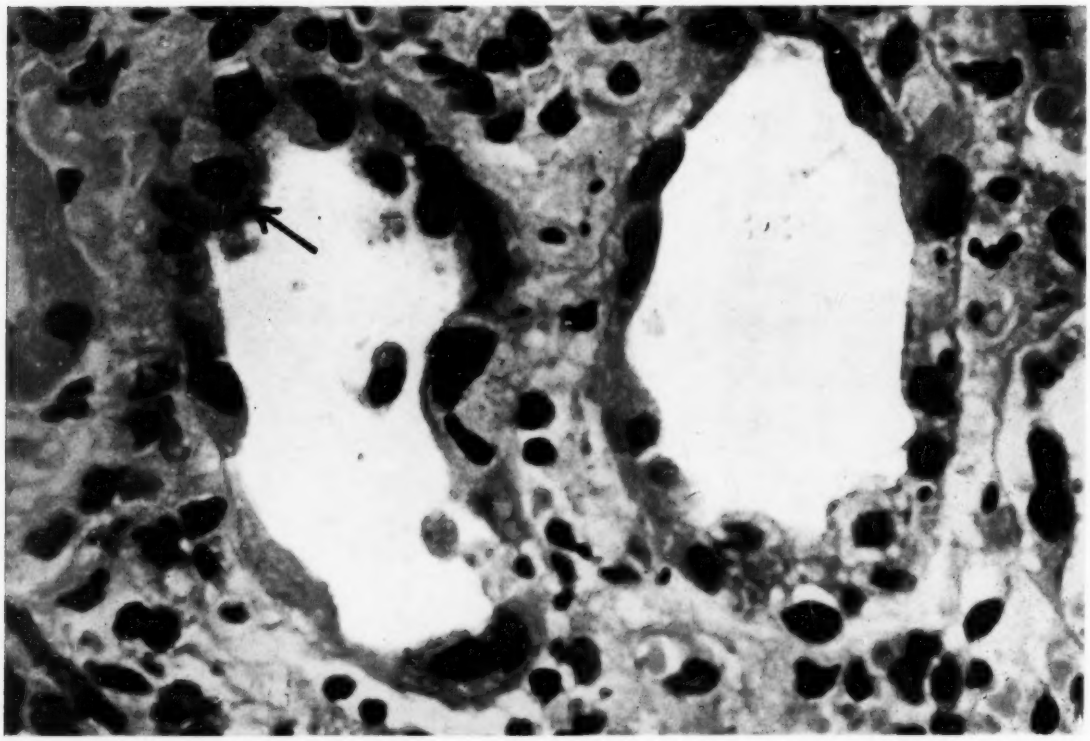


Fig. 7.—Kidney. Two regenerating convoluted tubules. Note the mitotic figure (top left corner of left tubule). (×1,092.)

Discussion

Dr. Milne: Sensitivity to drugs as a cause of renal tubular necrosis is rare. Perhaps it has been more commonly described with the sulphonamides than any other drug, but here it antedated his treatment with sulphonamides. We can only attribute it to the dindevan, and the anuria in combination with eosinophilia, a skin rash, and lymphadenopathy makes sensitivity very likely. The renal disease was resolving satisfactorily and he would have recovered had he not had such severe supra-diaphragmatic disease. I think the sepsis is explained by the fact that the uraemic patient is very liable to infection, particularly of dead or damaged tissue. This man happened to have a lot of damaged tissue in his body from pulmonary infarcts, and the combination of dead tissue and uraemia very easily gives rise to severe infection. I think one of the main reasons why traumatic renal failure has a bad prognosis is because of the tendency to infection of damaged tissue. Despite all our care, including avoidance of prolonged intravenous therapy, and barrier nursing, he got this infection, rather an unusual organism for the lung, a streptococcus, which I suppose was the eventual cause of death. To me, the great puzzle in this case is this man's primary lung lesion, and I hurriedly pass this over to my more learned colleagues.

Dr. J. F. Goodwin: I feel I should say something about Dr. Milne's comments and perhaps take them in order. The reasons for the original diagnosis of thrombo-embolic pulmonary hypertension were, I think, the following: When a previously well person develops signs of progressive pulmonary hypertension and at the same time, or previously, has pleuritic pain and haemoptyses, the diagnosis of pulmonary thrombo-embolism is almost certain. But unfortunately that isn't quite enough, because we want to know what is causing the thrombo-embolism, and in our experience the underlying conditions, when there are any, are either heart disease—usually mitral stenosis or atrial septal defect in this age-group—and conditions outside the heart such as recurrent thromboses in calf veins, giving rise to recurrent emboli; pulmonary micro-embolism* (which occurs sometimes after pregnancy and sometimes for no apparent reason at all); primary polycythaemia; and possibly rare forms of pulmonary arteritis.

This man had no evidence of mitral-valve disease, and no clinical evidence, so far as I can remember, of thrombosis in the calf veins or peripheral veins elsewhere. There was no evidence of a carcinomatous process such as we have seen followed by pulmonary thrombosis, so it was not unreasonable to wonder whether he had an atrial septal defect, since it is just at this age that patients with atrial septal defect tend to develop secondary pulmonary thrombosis. I was also attracted to this idea because when I saw him, particularly when he was anuric, I thought that his second heart sound was widely split and this also would have favoured the diagnosis. But at that time the chest radiograph was not available. Had I seen it, I should not have been so keen on an atrial septal defect because the right pulmonary artery wasn't really big enough. The systolic murmur would probably have been either a pan-systolic murmur due to tricuspid insufficiency secondary to pulmonary hypertension, or an ejection murmur as a result of the pulmonary hypertension itself, or of occlusion in the main pulmonary artery, but we now know that he didn't have that. I don't think the systolic murmur really helps regarding the underlying diagnosis.

The electrocardiograms were really classical of pulmonary thrombo-embolism, with T-wave inversion in precordial leads. The second tracing we were shown, I think, simply showed more marked effects of acute right heart embarrassment on top of chronic pulmonary hypertension. I wonder now—having seen the pathological findings—whether the sudden terminal collapse was due to pulmonary infection rather than to further pulmonary embolism. I think in patients with recurrent pulmonary embolism, particularly of the very small type involving the small pulmonary vessels, it is not uncommon at necropsy to find many more occlusions in the small vessels than you would suspect in life. I find it very difficult to understand why this man began to have this thrombotic process in his pulmonary vessels in the first place. Could he possibly have had a type of true polycythaemia? Another point is that if you stop anticoagulants suddenly, you are liable to get an increased tendency to thrombosis. Finally, this is, so far as I know, the first incidence of renal failure as a result of dindevan. It can produce rashes, but usually they are quite different from the sort of rash that this man had.

Professor J. McMichael: I saw this man in life but unfortunately failed to commit myself in writing, which is important if one is going to learn from mistakes. The murmur was a typical ejection-type murmur. Dr. Shillingford also documented the "diamond shape" ending before the second sound. We were disinclined to make a diagnosis of ventricular septal defect. It was clear that he had severe pulmonary hypertension and gross right-ventricular strain. The episodes seemed to be embolic. Professor Harrison's evidence is that the underlying basis of his pulmonary arterial lesion was emboli. Even although the veins were found to be clear of clot on detailed examination at necropsy, small emboli were lodging in vessels about 1 mm. in diameter. We must therefore think of venule thrombosis rather than an ordinary phlebo-thrombosis in the large veins as the start of his disorder. Small venules may have been overlooked in the post-mortem examination. It is difficult to account for his systolic murmur. It was a very significant clinical feature and I wonder if it could have been due to "whistling" in the partially occluded vessels in his lungs, rather than in his heart. There was nothing in his heart to cause it.

Dr. P. Shillingford: I don't think I have anything further to add. I am not able to explain it. It was an ejection murmur in type, heard best in the pulmonary area.

Professor McMichael: We never thought at any time that this was tricuspid incompetence, did we?

Dr. Shillingford: Not that I can remember.

Dr. C. M. Fletcher: Were any antibacterial drugs given after the sulphatriad was stopped? There was some evidence of infection. Why was no attempt made to control it?

Dr. Milne: We try to avoid prophylactic antibiotics and chemotherapy in acute renal failure, but if we find an infection, then, of course, we treat it. He never had pyrexia or signs of pneumonia, and he was therefore not treated with antibiotics.

*See last month's Clinicopathological Conference, "An Obscure Case" (*Brit. med. J.*, 1960, 2, 926).

Dr. R. E. Steiner: On the question of lung infection, the film you saw was the last film taken, 11 days before he died, and the lungs were then perfectly clear, so that all the extensive consolidation must have appeared between that time and his death. In the last few days this infection had spread much wider.

Dr. Milne: I think perhaps we should take more blood cultures whether cases are pyrexial or not. We do in our experience get a significant number of positive blood cultures in these patients without a pyrexial reaction, and perhaps it ought to be done more as a routine and more regularly. It is throwing a lot of work on to the bacteriological department, but they are never a department who complain about work—they revel in it.

Dr. Fletcher: May I ask one other question? There was clear evidence of recurrent embolism, and anticoagulant therapy was needed. He couldn't go on with dindevan because of sensitivity. Was any other anticoagulant considered? Are the dicoumarol group of drugs so closely related that you have to stop them all when you get a sensitivity to one? What about heparin? It seems to me that the patient was probably in need of continued anticoagulant therapy of some kind.

Dr. Milne: I think in retrospect that this man would have been best treated throughout his stay here with continuous heparin. This, I think, was a very unusual case, outside any of our previous experience. We have not previously seen acute renal failure as a complication of anticoagulant therapy for pulmonary emboli, and perhaps a therapeutic lesson is that continuous heparin should have been used. However, of course, it would have been technically a little difficult, as the incisions for dialysis, which he undoubtedly needed, are comparatively large and there would have been further haemorrhage from these. Of course, haemorrhage is always a complication of uraemia *per se*, so that I do not know if adequate control would have been feasible. I am not going to say dogmatically you are right, but I am willing to say you may be, and that it is worth a trial in a future case.

Dr. Goodwin: This was discussed before he had his first dialysis, and the feeling was that, as he was about to have a renal biopsy and a dialysis, those two factors seemed to contraindicate any form of anticoagulation at all. I certainly felt at that time (as Dr. Milne has pointed out) that the acute lethal condition was below the diaphragm, and that as anticoagulants had already been stopped they should not be restarted. One just had to hope that there wouldn't be any more thrombosis or embolism.

Dr. Milne: I should say that it would only contraindicate the renal biopsy, and I am sufficiently conservative not to regard renal biopsy as an essential in the management of acute renal failure.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

B.M.A. ANNUAL CLINICAL MEETING

MIDDLESBROUGH, OCTOBER 6–9

We reported last week (October 15, pp. 1147–51) the Scientific Proceedings on the first full day of the Association's Third Annual Clinical Meeting, held at Middlesbrough. This week we conclude our report with an account of the Scientific Proceedings on Saturday, October 8, and with a brief description of the industrial visits and the social arrangements.

SCIENTIFIC PROCEEDINGS

Saturday, October 8

In the morning there were Clinical Demonstrations at the Middlesbrough General Hospital. In the afternoon there were concurrent Symposia on "Bronchitis and Pulmonary Heart Disease" and on "Enterocolitis," followed after tea by a Transatlantic Clinical Conference on endocrine cases.

CLINICAL DEMONSTRATIONS

The clinical demonstrations were given by the consultant staff of the South Tees-side Group in Middlesbrough General Hospital, this being the largest and most central hospital of the Group. Demonstrations given by consultants not attached to this particular hospital were housed in the Out-patient Departments, Nurses' Training School, and *X*-ray Departments. There were 22 demonstrations and over 200 patients were asked to assist. Each demonstration was given three times and lasted 40 minutes, as at the Norwich Meeting. In some, cases were shown singly to illustrate short clinical lectures. In others, visitors were taken on ward rounds or invited to examine and discuss cases at leisure in the wards. Some demonstrations were designed more particularly to illustrate a technical manœuvre, and at these the number of visitors was of necessity restricted. Patently, great efforts had been taken to cater for as many clinical tastes as possible. Here it is possible to give only a brief summary of what was shown.

Dr. S. Wray and Dr. R. E. Potts dealt respectively with prostatic cancer and some aspects of the examination of blood in pregnancy. Dr. D. R. L. Newton demonstrated electro-diagnostic techniques. Dr. L. M. Shorvon showed how successful radiotherapy could be in certain forms of malignancy. Mr. E. Hoffman discussed some diaphragmatic disorders which he illustrated with cases and an impressive pictorial display. Mr. J. Potter showed examples of plastic surgery, while Dr. D. D. Webster discussed the psychiatric implications in some of these cases. Mr. F. S. Hubbersty and his colleagues enriched their demonstration of cases of cataract treated by extraction and, in some cases, by anterior-chamber implant with short films showing the techniques involved. Mr. P. R. R. Clarke and his team's demonstration of cerebral angiography was a popular feature, while Mr. G. Parker and his fellow orthopaedic surgeons attracted considerable interest with a series of cases with disorders of the hip-joint.

In general medicine Drs. A. A. Williams and F. O. Graham invited their visitors to examine and discuss a wide variety of cases in the ward, while Dr. C. E. Astley demonstrated neurological cases singly. Drs. J. J. Tillie and J. L. Greaves took limited groups

round the children's wards. Dr. D. M. PRINSLEY demonstrated the value of coagulation of the ventrolateral nucleus of the thalamus in Parkinsonism by showing a film of cases before operation and the cases themselves post-operatively. Dr. J. K. MORGAN took his visitors to see a large collection of dermatological cases in the ward. Dr. B. COUTS and his colleagues in the chest clinic showed a variety of cases, discussed problems such as air-pollution, and demonstrated equipment. On the surgical side Mr. D. C. DICKSON and Mr. J. C. CLARK showed patients who had had major surgical operations, their demonstration being enlivened with the projection of colour transparencies and histological sections. Mr. S. MOTTERSHEAD performed paravertebral block in a demonstration of peripheral vascular surgery. Mr. E. W. GRAHAME and Mr. G. E. FORDYCE also showed interesting surgical cases. Mr. BRYAN WILLIAMS and his colleagues provided a remarkable series of uterine deformities and also a varied collection of interesting gynaecological cases. Finally the programme was completed by the Tees-side team of anaesthetists, who staged demonstrations of anaesthesia for minor surgery, dental surgery, and orthopaedic manipulation, and showed new equipment for use in chest surgery (Dr. G. M. J. WHITE).

Microscopic preparations of a high standard featured in several demonstrations and had been set up by the pathological department, while the radiological department had gone to great lengths to help with the many radiographs on show. The hospital was well signposted and well stewarded by a large body of volunteers from the local school of radiography. Coffee was served during the second interval. All this contributed to a very pleasant morning, much enjoyed by the large number of visitors who attended.

SYMPOSIUM ON BRONCHITIS AND PULMONARY HEART DISEASE

At the Town Hall after lunch there was a symposium, with Dr. M. WALTON (Middlesbrough) in the chair, on several aspects of bronchitis and its unfortunate sequelae. Professor C. H. STUART-HARRIS (Sheffield), outlining the economic consequences of bronchitis, said it was called the "English disease" because it was so much more common here than in the rest of Europe. In the United Kingdom alone it was estimated that each winter some 15,000–20,000 people lost their lives from bronchitis. The mortality was 50 times as great as in Norway. The disease was difficult to define. It was thought that some clinical account of it had been given by Assyrian physicians several thousand years ago, and Laennec was certainly fully aware of the disease. In Britain chest physicians had until fairly recently been more concerned with tuberculosis, but now their attention was turning more and more to bronchitis. The sort of patient most physicians had in mind was the middle-aged or elderly man with a cough, expectoration, and breathlessness, especially in the winter. But in the early stages there was no breathlessness, and, of course, the production of phlegm might result from many causes. One had first to exclude focal structural lesions of the bronchial tree such as bronchiectasis. The patient might deny that he brought up sputum, but in fact he always could produce some if required. Histologically there was an increase in the goblet cells of the bronchial mucosa, and the accumulation of mucus was one of the causes of the wheezing that was present intermittently in many cases.

Professor Stuart-Harris emphasized the importance of bronchial obstruction resulting from mucosal oedema, mucus, and anatomical changes in the bronchi. This led to hyperinflation and thereby to emphysema. In asthma the bronchial obstruction was always intermittent and usually reversible under the influence of drugs, so that asthmatic subjects might not, indeed often did not, develop emphysema. The presence of local disease in the bronchial tree or in the lung parenchyma did not of course exclude bronchitis, and it was not uncommon to find two conditions coexisting—for example, pneumoconiosis and bronchitis. One of the early definitions of emphysema recognized the increased residual air that was characteristic. The important increase was in the calibre of the air passages distal to the bronchioles. As to the aetiology of bronchitis, there was no doubt that it was multifactorial. In some cases there might be a local anatomical fault arising in childhood, but consideration of the question of cause must recognize the fact that the condition was much less common in women at all ages up to 65. Infection played an important part, including that due to viruses such as the common-cold virus, and, of course, influenza. Of importance also were bacterial infections, atmospheric pollution, living in towns, overcrowding, and the other circumstances affecting those in the Registrar-General's Social Class V, and constitutional factors such as allergy. The last of these was much stressed in the European literature, though there was some doubt about its importance. Cigarette-smoking was known to be an important factor.

Catarrhal Children

Mr. H. ZALIN (Liverpool), speaking as an otorhinolaryngologist, stressed that the seeds of chronic bronchitis were sown in childhood. In support of this he pointed to the frequent association of upper and lower respiratory disease—for example, sinusitis and bronchiectasis. The worst geographical areas for bronchitis were in the North of England, where also chronic ear disease was most common. The danger period in childhood was especially during the first two years of school life, when the child was exposed to many infections. In the first stage the child was subject to colds and catarrh. This led to the second stage, of lymphoid hyperplasia, which in turn led to permanent nasal obstruction. In the third stage more serious disease became established—sinusitis, otitis, bronchitis, and bronchiectasis. The first two stages were easily treated and arrested and the condition might clear up, but the third stage was much more difficult to manage.

Mr. Zalin thought that 50% of those with purulent infection of the antra also had bronchiectasis, and he considered that otitis was to the upper respiratory tract what bronchiectasis was to the lower respiratory tract. Regarding aetiology, he considered the overcrowding of poverty exposed a child to infection from birth. Three other factors were of importance—atmospheric pollution, virus and bacterial infection, and allergy, especially to inhaled allergens. In the treatment of chronic ear infections Mr. Zalin stressed the importance of adequate treatment with antibiotics for a period of three weeks. In the treatment of sinusitis he advised intranasal instillation of antibiotic in Ringer's solution, and he strongly deprecated the use of vasoconstricting agents.

Air Pollution

Dr. P. J. LAWTHER (London) gave a witty account of the work of his atmospheric pollution study group at St. Bartholomew's Hospital. He made the major point that domestic fires provided most of the polluting smoke at lung level. Although most investigations measured the amount

of pollution in a 24-hour period, real danger came from high peaks of pollution of much shorter duration. Fog and smoke might occur separately or together, in the latter instance giving rise to the term "smog." Microscopically smoke particles were only one of the items found. Others included crystals of ammonium sulphate, and semi-solid particles consisting of a nucleus surrounded by sulphuric acid had been discovered to be most important. The size of the particles in most instances was less than one micron, and the electron microscope had been of great value in depicting them. Some of the particles were combustible, consisting of carbon molecules. Others were not—for example, sodium chloride molecules. Many of the particles were shown to be branched, but the important fact about them was that they could all penetrate to the alveolus. One form of pollution that was easily prevented was that due to cigarette-smoking.

Pulmonary Heart Disease

Dr. RAYMOND DALEY (London) discussed the mechanics of cor pulmonale or, as he preferred to call it, pulmonary heart disease. This condition resulted from the obstruction to the flow of blood through the lungs from kyphoscoliosis, emphysema, obstruction to the pulmonary vascular tree, etc. In addition to obstructing the blood flow, emphysema interfered with air flow, gas exchange, and, of course, alveolar ventilation. Carbon dioxide was retained, arterial anoxia developed, leading to cyanosis. The rise in pulmonary-artery pressure had been shown to be the result of the fall in alveolar oxygen concentration, and transient acute rises in pressure had been found during acute attacks of bronchitis. It seemed to be the arterial anoxia that led to the rise in pulmonary arterial pressure, for experiments had shown that if the partial pressure of oxygen in the alveoli was lowered, but the arterial oxygen saturation artificially maintained, there was no rise in pulmonary-artery pressure. In cor pulmonale the renal blood flow was reduced. The bone-marrow responded normally to the anoxia by producing more red cells, but the haematocrit reading often remained unchanged because there was a corresponding increase in the plasma volume. In the later stages the cardiac output fell, and there was peripheral vasoconstriction.

In treatment, in addition to antibiotics and bronchodilators, Dr. Daley advised the use of oxygen intermittently, and he referred to the use of tracheotomy with intermittent bronchial suction. Of the diuretics, he considered the chlorothiazide group most valuable. He personally thought that digitalis ought to be used, though not in the early stages. Where the venous pressure had risen greatly and the cardiac output was falling, venesection might be carried out. Finally, he referred to the use of antithyroid treatment to control the twitching that was a feature of the advanced disease.

[Evening Gazette, Middlesbrough

Dr. Solomon Wand, chairman of Council, being greeted by Dr. J. B. S. Guy, chairman of the Cleveland and Middlesbrough Division, and Mrs. Guy, at the Division Reception.

SYMPOSIUM ON ENTEROCOLITIS

The second symposium, on the medical, radiological, and surgical aspects of enterocolitis, was held in the Municipal Buildings under the chairmanship of Mr. D. C. DICKSON (Middlesbrough).

Medical Aspects

Dr. R. H. GIRDWOOD (Edinburgh) thought that enterocolitis embraced a variety of conditions, including staphylococcal and tuberculous ulceration, ulcerative colitis with ileal involvement, Crohn's regional enterocolitis, and a type of non-specific enterocolitis described in Birmingham some years ago. Many of these diseases produced intestinal malabsorption with multiple deficiency states, and it was with this aspect of the problem that the speaker was mainly concerned.

Malabsorptive states might result from coeliac disease, from idiopathic steatorrhoea, from tropical sprue, or be symptomatic of a variety of organic conditions of the small intestine, including tuberculosis, Crohn's disease, resection, diverticuli, blind loops, and fistulae. It could complicate gastric operations and pancreatic and liver disease. It followed that investigation of this syndrome must be detailed and complex, and should include examination of the faeces for content and occult bleeding; absorption tests using glucose, xylose, folic acid, and labelled cyanocobalamin; and haematological assessment by blood count, examination of the bone-marrow, and estimating the serum B_{12} levels. Structural disease might be demonstrated by radiological studies or sigmoidoscopy, and bone disease should be excluded by investigation of blood levels of calcium, phosphorus, and alkaline phosphatase. Jejunal biopsy, employing the Crosby tube, was thought to be the most helpful investigation in that if villous atrophy or deformity were demonstrated a diagnosis of a primary malabsorption disorder could be made. Unfortunately he had seen several patients with primary disorders in which the normal anatomy had been preserved. Despite the use of this formidable battery of investigations it was not always possible to establish a final diagnosis. In treating steatorrhoea in children and adults, the gluten-free diet had established itself as a valuable therapeutic measure, but it was irksome to maintain and overexpensive for the patient. Dr. Girdwood felt that gluten-free flour, a substance prepared exclusively for the treatment of this disease, fell within the official classification of a drug rather than a food and should be prescribable.

Radiological Diagnosis

Professor A. S. JOHNSTONE (Leeds) reviewed the radiological changes. Ulcerative colitis, as it usually involved the rectum initially, was readily diagnosed by direct inspection. But radiology became necessary to demonstrate the extent and severity of the lesion, or it could be used serially to demonstrate the effects of treatment or the development of complications such as fibrosis, stricture, perforation, toxic dilatation, and carcinoma. The recognition of the advanced case presented no problems, the bowel being narrowed, of irregular outline, and often showing polyps or

local stricture formation. The detection of the earlier inflammatory changes was more difficult. Often a fine irregularity of the lumen of the bowel could be recognized, resembling "torn cardboard," while a lateral radiograph might demonstrate increased space between sacrum and rectum due to perirectal oedema. In acute cases giant ulceration might give the fallacious impression that haustration of the colon was preserved, while spasm in an inflamed segment of the bowel might cause proximal dilatation and faecal loading. Right-sided or segmental inflammatory colitic disease could be demonstrated only radiologically, but it could be confused with Crohn's disease or the atonic bowel which accompanied habitual catharsis. Radiological differentiation of true segmental ulcerative colitis from Crohn's disease involving the colon had not proved feasible. The radiological demonstration of the ileal lesions of Crohn's and other diseases involved the use of a barium meal and follow-through examination. Better visualization of the small bowel was obtained by introducing barium and glucose through a tube which had been passed into the jejunum. Professor Johnstone emphasized the necessity of adequate preparation for the radiological examination. He felt that general practitioners could help a great deal in ensuring this had been carried out by out-patients attending hospital.

Preservation of Rectum and Anus

Mr. STANLEY AYLETT (London) gave an account of his experience of the value of total colectomy followed by ileorectal anastomosis in the treatment of diffuse ulcerative colitis, which he and his colleagues at the Gordon Hospital had used in the treatment of this condition since 1952. Their favourable experience had convinced them that the majority of colitic patients were treatable by this method and that ileostomy and proctocolectomy was necessary in less than 5%. To date 161 patients had been operated upon with an overall mortality of 5%, despite the fact that 31 of these patients had fulminating and 69 acute disease. Three patients had died subsequently, two of carcinoma in the rectal stump. Nine out of ten of surviving patients returned to normal health, the mucosa in the rectal stump being capable of amazing recovery and healing. While some of these patients had frequent bowel actions, averaging 4–6 daily, this was thought to be a small price to pay for the preservation of rectal continence.

In discussing indications for operation, the speaker felt that all acute cases should be treated medically initially, but that surgery should not be delayed unless improvement was early and sustained. In his experience physicians tended to delay operation for dangerously long periods. Biochemical evidence of liver disease indicated a serious prognosis and was another indication for operation. Neither rectal stricture nor polyposis contraindicated operation. Lack of attention to details of technique was thought to explain the failure of other clinics to get comparable results. Mr. Aylett emphasized that an immediate anastomosis should never be attempted in the gravely ill patient, that the ileorectal anastomosis should be protected by a proximal defunctioning ileostomy, and that the vascularity of the rectal stump should be reduced by severing the superior haemorrhoidal artery. Many post-operative complications had been experienced, of which obstruction was the most common, but had been successfully dealt with by a trained team of nurses and doctors.

Total Colo-proctectomy

Professor JOHN BRUCE (Edinburgh) was not convinced that ileorectal anastomosis was the procedure of choice in diffuse colitis, in that it was often followed by troublesome diarrhoea and left the rectal stump in which a carcinoma might develop. Good results were obtained in segmental colitis or in the few diffuse cases in which rectal involvement was not severe. He therefore favoured total colo-proctectomy with ileostomy, a procedure readily accepted by the majority of colitic patients, particularly if allowed to discuss the operation with a patient with an ileostomy. Surgery was indicated where chronic disease had produced ill-health, prolonged uncontrollable diarrhoea, severe systemic complications such as arthritis or iritis, or where colonic complications such as stricture, perforation, severe polyposis, or suspected carcinoma had developed. Colitic patients had been shown to develop carcinoma between seven and ten times as commonly as normal subjects. New methods of medical treatment had made it unusual to have to operate in acute fulminating attacks, but he emphasized that improvement should be apparent within a week of starting therapy, and that physician and surgeon should work in close co-operation if good results were to be obtained.

In the lively discussion that followed, both speakers agreed that operation was not desirable in all patients purely to prevent a carcinoma developing. Both surgeons felt that temporary ileostomy had no place in treatment even in the most desperate of attacks. They differed in their interpretation of the causes of "toxaemia" in colitic patients, Mr. AYLETT favouring absorption of the toxic products of inflammation, and Professor BRUCE protein depletion. The value of sulphasalazine and topical steroids in medical management was also emphasized by other speakers.

TRANSATLANTIC CLINICAL CONFERENCE

After tea on Saturday there was a transatlantic discussion on endocrinological cases. The two panels of experts, the British in Middlesbrough Town Hall and the Americans in Philadelphia, were linked by transatlantic telephone. In the Town Hall there were giant photographs of the members of the American panel and as each spoke a red light went on over his photograph. This remarkable demonstration of long-range consultation was made possible by the kindness of Messrs. Smith Kline and French Laboratories Ltd.

The British panel consisted of Dr. RAYMOND GREENE (London), chairman, Dr. C. N. ARMSTRONG (Newcastle upon Tyne), Dr. C. L. COPE (London), and Dr. A. STUART MASON (London). In Philadelphia the American

[Evening Gazette, Middlesbrough

The chairman and speakers at the General Session on Friday morning (see *Journal*, October 15, p. 1149). From left to right, Mr. J. J. Mason Brown, Mr. Harold Walker (chairman), Dr. C. S. Nicol, and Dr. W. W. Sargant.

panel were introduced by Dr. G. C. ENGEL, professor of clinical surgery at Pennsylvania University. The panel comprised Dr. A. E. RAKOFF, clinical professor of gynaecologic endocrinology, Jefferson Medical College, moderator; Dr. EDWARD ROSE, professor of clinical medicine, Pennsylvania University; Dr. W. H. PERLOFF, endocrinologist, Albert Einstein Medical Center; and Dr. A. M. BONGIOVANNI, associate professor of paediatrics, Pennsylvania University. The conference liaison officer was Dr. R. BLOWERS (Middlesbrough).

After a preliminary exchange of greeting the British problem case was presented by Dr. RAYMOND GREENE.

British Case

The patient was a female aged 28 who presented in July, 1951, with complaints of staring eyes, a swollen neck, and hirsuties on the front of her legs, all of which dated from the birth of her first child six months previously. There were no other symptoms of thyroid disorder. In her past history there was a story of a sudden increase in weight, from 177 to 219 lb. (80.3–99.3 kg.), between 1942 and 1944. For this she was treated with thyroid and a diet and her weight dropped to 168 lb. (76.2 kg.). It increased after her pregnancy to 183 lb. (83 kg.) and by the identical treatment was later reduced to 169 lb. (76.7 kg.). She was being maintained on thyroid, ¾ gr. (50 mg.) daily, at the onset of her symptoms. There were no menstrual abnormalities. She had a paternal aunt who suffered from thyrotoxicosis.

On examination she had a pronounced stare due to upper-lid retraction and there was some puffiness of the lids. Clubbing of the fingers and slight pretibial myxoedema were also noted. She had a small, hard goitre which in consistency could have been due to Hashimoto's disease. There was no other evidence of thyroid abnormality and no other abnormal physical signs. As a result of a diagnosis of Hashimoto's disease she was advised to increase thyroid to 3 gr. (0.2 g.) daily, but her exophthalmos, pretibial myxoedema, and clubbing became worse. She was therefore fully investigated. Hypothyroidism was confirmed both biochemically, by E.C.G., and by skin biopsy. Radiographs of her hands showed some periosteal new-bone formation. Despite increased dosage of thyroid her presenting symptoms became worse while her general condition improved. She likewise failed to respond to many other forms of treatment.

In 1954 her myxoedema relapsed and it was necessary to raise her thyroid intake to 12 or 15 gr. (0.78–1 g.) a day to avoid symptoms. Thyroid "analogues" likewise had very disappointing results. This insensitivity to L-thyroxine and triiodothyronine resulted in further investigations, which showed that absorption was normal but that there was a true insensitivity of the tissues.

American Assessment of British Case

Following the presentation of the case, the American team asked several questions designed to discover whether there was any previous history of thyrotoxicosis, any suggestion of pituitary deficiency following parturition, any chest disease, or any other evidence of myxoedema. To all of these questions Dr. GREENE was able to give a negative answer. Dr. ROSE then discussed the differential diagnosis. He considered that it was established that this was a case of hypothyroidism associated with an auto-immune reaction. He discussed the possible reasons for local tissue susceptibility in the pretibial area to thyrotrophic hormone, pointing out that this condition was usually preceded by a history of thyrotoxicosis with ophthalmopathy. The resistance to the various forms of replacement therapy might have been due to an enzyme defect, and in any event there were very great individual variations in susceptibility to such treatment.

The final summary was given to Dr. COPE, who pointed out that the resistance to the treatment with thyroid substances could not have been due to an antithyroglobulin since it was just as pronounced when non-protein-containing preparations were given. It was important to observe that the suppression of thyrotrophic hormone was not followed by regression of the pre-tibial myxoedema or exophthalmos.

American Case

The American problem case was presented jointly by Dr. RAKOFF and Dr. PERLOFF.

The patient was a 19-year-old boy complaining of maldevelopment of his genitalia and failure of other secondary sexual characteristics. He was born by a normal delivery, but during his infancy his mother noted failure of development of the genitalia, and at the age of 12 exploration failed to reveal any gonads. His general development up to the age of 14 was fairly normal, although it was noted that his facial hair was sparse and fine. His physical and psychological traits were now essentially masculine and he was of high intelligence. In the last eight months he had suffered from three episodes of terminal haematuria. Cystoscopy showed a urethral diverticulum and the absence of prostate. Retrograde pyelograms were normal. On examination his height was 63 in. (1.6 m.) and he weighed 120 lb. (54.4 kg.). The facial hair was sparse and very fine. The phallus was small and of hypospadic configuration. The scrotum was poorly developed and no testes were palpable. Per rectum no prostate or seminal vesicles could be felt.

Full investigation of the blood revealed no abnormalities. Radiography showed a normal bone-age but there were multiple minor spinal abnormalities and an android pelvis. Smears for chromosomal sex showed a "female" pattern. The 17-ketosteroids were raised (46.8 mg. per 24 hours) on one occasion but considerably less on subsequent estimation. Oestrogens were less than 12 m.u. per 24 hours, pregnanetriol was considerably raised at 15 mg. per 24 hours, and his corticoids were 2.3 mg. per 24 hours (Porter–Silber method). He was examined by a cystoscopy and an orifice 4 mm. in diameter was found just beyond the external urethral sphincter. Examination of this orifice revealed a capacious vagina with an atrophic type of cervix. The bladder itself was normal. The psychiatrist reported predominantly male psychosexual interests.

An exploratory operation revealed a small uterus with cystic ovaries. The adrenals appeared normal to palpation. A salpingo-oophorectomy was performed and testicular prostheses (20 mm. vitallium spheres) inserted. A plastic operation was performed on the penis. Histology of the ovarian tissue revealed numerous Graafian follicles and multiple cysts. He was currently being treated with testosterone for hot flushes. This had resulted in the development of acne, but there was an increased growth of facial hair and increase in the size of the phallus.

British Assessment of American Case

Dr. GREENE inquired whether by any chance the haematuria showed a cyclical tendency—that is, whether it could have been a menstrual phenomenon. The reply being that this was not so, questions were asked about the mode of micturition, which was male; the site of opening of the urethra, which was in the glans; and whether the iliac crest epiphysis had closed, which it had. Dr. COPE inquired provocatively about the very considerable differences in the biochemical results done on separate occasions. He wondered if by chance the patient had received any treatment, or if, perhaps, he had attended a different hospital. The American team had no explanation for these variations but assured us that they had been carefully checked. Dr. ROSE wondered whether hydrocortisone should have been given, since the high pregnanetriol level indicated an inability of the patient's adrenal to complete the synthesis of this hormone. It had in fact been given to cover the operation and the patient had been warned that he would need it in the event of future stress.

Discussing the differential diagnosis, Dr. ARMSTRONG wondered whether possibly the mother had received any hormone during pregnancy. He also discussed the possibility

of a congenital virilizing adrenal hyperplasia. He excluded the Stein–Leventhal syndrome and also true hermaphroditism, the latter because no one had discovered any true testicular tissue. He pointed out that the determination of this patient's true sex might have considerable medico-legal implications and wondered if, for example, his father had been the Duke of Philadelphia the patient could have inherited the title from him. There might also be legal implications in the event of apparent homosexual behaviour. Dr. RAKOFF, in summarizing the case, pointed out that one lesson at least could be learned from it—namely, the importance of obstetricians and paediatricians examining infants at birth to ensure that their gonads were normal. Early treatment of the adrenal hyperplasia in a case such as this might well have prevented the development of the full syndrome, and now that nuclear sexing was a relatively simple matter there could be no excuse for neglecting this.

INDUSTRIAL VISITS

On Saturday afternoon visits were paid to the Billingham and Wilton Divisions of Imperial Chemical Industries Ltd., and on Sunday morning there were the alternatives of a visit to the Lackenby Steelworks of Dorman Long and Co., Ltd., or a trip on the River Tees by courtesy of the Tees Conservancy Commissioners.

A party of 33 went to Billingham Works, where they were welcomed by the chairman of the Billingham Division, Mr. W. J. V. WARD. Dr. T. S. SCOTT then gave a short talk on the profession's responsibility to workmen, especially where working with dangerous materials. Some industries, such as those concerned with coal, atomic energy, and insecticides, which were essential to the country, had a high rate of hazard, and the industrial medical officer had a duty to keep the workmen informed of the risks. Mr. C. W. LOFTHOUSE then took the party on a conducted tour of the works, visiting the sulphuric acid, cement, nitrogen, and hydrogen plants. Dr. F. H. C. BEARDS, the senior works medical officer, and his colleagues demonstrated the new medical department, explaining the record system and showing the dental, physiotherapy, and M.M.R. departments. In the laboratory the various techniques, including cytology of the bladder, for investigating industrial hazards were demonstrated.

The 50 visitors who went to Wilton Works were greeted by the chairman of Wilton Council, Mr. J. C. H. MCENTEE, the works manager, Mr. GRANGE MOORE, and the senior medical officer, Dr. S. JENKIN EVANS. Dr. A. LLOYD POTTER, principal medical officer of Imperial Chemical Industries Ltd., in an address on the present and future of industrial medicine, stressed the importance of close liaison with the general practitioner and suggested an additional grade—that of trainee industrial medical officer—to the B.M.A.'s classification of I.M.O.s. Visits were then made to the Terylene plant, the power station, and the medical centre. At the medical centre the demonstrations included air-sampling techniques, columetric analysis of chemicals in urine, and the accident-prevention organization. At both the I.C.I. Divisions excellent buffet meals were provided.

On Sunday over 100 people were the guests of Dorman Long and Co., Ltd. They were welcomed by the managing director, Mr. E. T. JUDGE. A visit was made to the Clay Lane Works to see the blast furnaces, and one was tapped while the visit was in progress. Other parties went to the jetties to see the unloading of the ore and to inspect the coke ovens. At Lackenby Steel Plant a steel furnace was being tapped. Again the visitors were most hospitably entertained.

SOCIAL OCCASIONS

No report can do justice to the open-handed hospitality of the Cleveland and Middlesbrough Division, the Civic Authorities, and the Ladies' Committee at Middlesbrough. In addition to this, all the visiting speakers, and some other visitors also, were accommodated by individual doctors in the neighbourhood. There were two major receptions, both at the Town Hall and both crowded to overflowing: that given by the Mayor and Corporation of Middlesbrough on the first evening (reported last week), and the reception given by Cleveland and Middlesbrough Division on the Friday evening. At this, a most notable champagne party, the guests were graciously received by Dr. J. B. S. GUY, chairman of the Division, and Mrs. GUY. On Saturday evening there was a cocktail party at the Corporation Hotel, followed by a special performance at the Little Theatre of John Mortimer's play, "The Wrong Side of the Park."

No account of the social side of the Middlesbrough meeting would be complete without mention of the programme arranged for visiting wives by the local Ladies' Committee under Mrs. J. C. CLARK. This included a luncheon, a visit to a clothing factory, and coffee and sherry parties.

Recrudescence of Venereal Disease.—Dr. C. S. NICOL (St. Thomas's Hospital, London S.E.1) writes: A number of points I made in my paper on "The Recrudescence of Venereal Disease" at the Clinical Meeting at Middlesbrough have been misinterpreted in your report (October 15, p. 1149): (1) New cases of lymphogranuloma venereum, granuloma inguinale, and non-gonococcal urethritis in the male *are* included in the clinic returns to the Ministry of Health, but these conditions are not considered to be venereal diseases in the eyes of the law. (2) The Ministry of Health returns do not indicate the true prevalence of venereal diseases because cases treated by general practitioners or by consultants in private practice are not included. (3) The suppression of the signs and symptoms of syphilis by the widespread use of antibiotics in undiagnosed cases may partly explain the decrease in the official figures in recent years. (4) New blood tests (T.P.I. and R.P.C.F.) make the diagnosis of late syphilis more accurate and prevent the misdiagnosis of false-positive reactors. (5) The immigrant group mentioned as one of the possible causes for the marked increase in cases of gonorrhoea are usually infected *after* their arrival in Great Britain. (6) Reiter's syndrome is always associated with a non-gonococcal urethritis. It is very rare to find the *T. vaginalis* in this condition. (7) It is believed that *T. vaginalis* infection is usually sexually transmitted. It is more difficult to identify the organism in the male, but careful investigation may increase the percentage. (8) A new oral drug, metronidazole ("flagyl") is available for the treatment of trichomoniasis; in adequate doses it cures the majority of female patients. Male sex-contacts with infection are also given similar treatment.

NEW ACADEMIC YEAR

ROYAL FREE MEDICAL SCHOOL

The annual ceremony marking the start of the 1960–1 session of the Royal Free Hospital School of Medicine was held on October 5 at the Senate House of London University. In his inaugural address, Sir IFOR EVANS, Provost of University College, London, took as his theme: "The Practitioner in the Modern World." As a layman, he said, he felt somewhat ill-equipped to discourse upon such a formidable subject, though close ties had always existed between those in the medical and literary fields. Students embarking upon a medical career would be well advised to take a particular interest in the history of medicine. For instance, the case records of William Smellie, the eighteenth-century gynaecologist, whose works were edited by another doctor, Smollett, contained much of value for the medical student.

Practice in the Modern World

The present period was a crucial one for those entering the medical field, and it was for that reason, Sir Ifor said, that he had chosen the particular title for his address. Students attending the Royal Free Hospital School of Medicine had a great heritage; University College had, by its establishment in 1828, led the way in the history of university medicine in England (although, in Scotland, medical education had started a century before). Those who had inherited that tradition should now hold as their twin aims the pursuit of the great and humane tradition of medicine and, at the same time, the advancement of its scientific aspects. In a century marked by violence and where much in civilization could be challenged, it was

encouraging to recall the great advances made in the conquest of disease since the beginning of the nineteenth century. That was due both to the development of the sciences and to improved knowledge relating to diagnosis, care, and treatment. Medicine was, in effect, the correct working of an art within a science.

Presenting her report on the previous year's work, the Dean of the School, Dr. K. LLOYD-WILLIAMS, said that during the previous year an interchange of teaching staff had taken place between the United Kingdom and the United States. Such exchanges were beneficial to the countries concerned and befitted a school responsible for training doctors for service overseas. Demolition work in preparation for the erection of the new hospital at Hampstead was scheduled to start next year.

CHARING CROSS MEDICAL SCHOOL

The opening-day ceremony and prizegiving of the Charing Cross Hospital Medical School was held at the Senate House of London University on October 13. Lord PIERCY, chairman of the Industrial and Commercial Finance Corporation, Ltd., and president of the National Institute of Industrial Psychology, delivered the inaugural address.

Addressing himself particularly to those who were "stepping out into a great and noble profession," Lord Piercy recalled that medicine was a profession with an ethical basis. From the earliest time the qualities of integrity, disinterestedness, candour, and sympathy had been expected in the medical practitioner, and underlying all that the observance of the principle of the sanctity of human life. Medicine, in addition to being a science, was a philosophy.

Medicine as a Social Function

Lord Piercy then spoke on two aspects of the current history of medicine—the content and the institutions of medicine. On the institutional side, the great feature of the present time was the nearly universal recognition of medicine as a social function which the community must provide. He recalled that two or three years ago, when he was in the United States, there was excitement in that country about what they called "social medicine," and he had committed several social blunders before he discovered that to many Americans it was a bad word. But even in the United States social medicine was now making its way, and it must do so because of the great populations. It could do so to-day because in something like a hundred years that vast instrument, the modern State, had been created—something new in world history, with immense resources and powers. The State was steadily taking over the provision of medicine. That was why for some years now we in this country had been wrestling with the complexities and, perhaps, crudities of the National Health Service. The fact remained, however, that in the present day the conjunction of the new knowledge and the great resources which were at the command of medicine opened out wonderful perspectives and opportunities for the new generation of doctors.

Lord Piercy reminded his audience that Charing Cross Hospital was an example of that very remarkable phenomenon the voluntary hospital, an institution set up and maintained by philanthropic support and the great devotion of the profession. It was at the same time a teaching hospital. The voluntary hospital, with the teaching hospital and the medical school which it had generated, was the model for all modern institutionalism, and provided one of its main structural elements.

The Dean, Professor W. J. HAMILTON, referring to the rebuilding of Charing Cross Hospital at Fulham, said that much of the preliminary planning had been completed, block designs had been prepared, and the day could dimly be discerned when the foundation stones of the new hospital and medical school would be laid. In the meantime the site at Fulham was being cleared, and temporary buildings were being erected to enable the development programme to go ahead during the transitional period of rebuilding. To that end prefabricated laboratory accommodation had been erected to house the new medical unit and to provide a footing at Fulham for the surgical and obstetric units.

AMERICAN PATHOLOGISTS IN CONGRESS

[FROM A SPECIAL CORRESPONDENT]

The joint annual meeting of the American Society of Clinical Pathologists, the College of American Pathologists, and the Inter Society Cytology Council was held between September 23 and October 2 at the Palmer House, Chicago. Over 2,000 pathologists attended the meeting, which included 48 reports on research, 71 technical and 27 scientific exhibits, 33 workshop courses in complex laboratory procedures, and a one-day seminar devoted to diseases of the lower face, including the salivary glands. Selected contributions are reported here.

Platelet Formation in Lungs

Dr. G. SHARNOFF, pathologist to the Mount Vernon Hospital, reported that the lungs were an additional site of platelet formation. Previously it had been thought that platelets were formed only in the bone-marrow from megakaryocytes. However, all mammals he had studied to date had been shown to transport megakaryocytes under normal conditions to the lungs, where they broke up to form platelets. Under various stress conditions the megakaryocytes were noticed to break down suddenly and more rapidly into platelets, thus increasing the number of platelets in the blood (thrombocythaemia). The degree of platelet increase depended on the number of megakaryocytes in the lungs at any given time. The resultant abnormal clotting was noted whether or not any disease such as atherosclerosis was present. The importance of these findings was that they might offer a more rational approach to the prevention of abnormal blood-clotting in potentially fatal conditions such as coronary thrombosis, post-operative pulmonary embolism, and cerebral thrombosis.

Oral Cancer

Dr. B. CHOMET, of Chicago, stated that some 80% of the 3,700 annual deaths in the U.S. from cancer of the mouth could be prevented by early recognition and prompt treatment. Whereas the oral cavity should be an ideal site for the recognition of the early stages of oral cancer, including intra-epithelial and early invasive growths, few cases where such lesions had been discovered had been reported. He stressed the need for increased awareness on the part of dentists of manifestations of oral malignancy, and suggested more extensive reference to physicians for biopsy as an important preventive factor. Oral cancer now accounted for 3% of the cancer mortality in the United States. Thorough oral examinations had been given to 10,178 patients in the past year at the Veterans Administration West Side Hospital, and had resulted in the finding of 32 malignant growths, of which 22 were in the early stages.

Nickel in Tobacco Smoke

Dr. W. SUNDERMAN, of Philadelphia, referred to British reports on lung cancer in nickel workers, and said that heavy smokers of cigarettes inhaled amounts of nickel, derived from the soil, in excess of that found to cause pulmonary carcinoma in rats. A person smoking two packs of cigarettes a day (the standard American pack contains 20 cigarettes) would inhale about 5,400 μg. in a year. Tobacco smoke provided a ready means of transporting an active form of nickel into the respiratory system. Nickel had a great affinity for carbon monoxide, which was formed in the burning of tobacco. Nickel or nickel compounds in a finely divided state would unite with carbon monoxide to form nickel carbonyl, even at environmental temperatures. Maximum concentrations were obtained at 45–50° C., which

was within the range of the temperature of the combustion of gases from burning cigarettes. Six different brands of cigarettes were studied. The amount of nickel recovered varied from 1.59 to 0.07 μg., and the mean for five non-filter brands was 1.99 μg. Seventy-one per cent. of the nickel was recovered in the ash and butt, 20% in the mainstream smoke, and 8.6% in the sidestream smoke. If an individual smoked two packs (that is, 40 cigarettes) a day for a year and inhaled all the mainstream smoke, he would inhale approximately three and a half times the amount of nickel shown to be carcinogenic for rats. These findings suggested that efforts should be made to remove the nickel from cigarette smoke.

Necrosis after Antibiotic Injections

Dr. D. J. Hanson, of Toledo, Ohio, described the results of an experiment in which various antibiotics—oxytetracycline, oxytetracycline in propylene glycol, tetracycline, chloramphenicol, and chloramphenicol succinate — were injected subcutaneously or intramuscularly in single or repeated injections into rabbits. The most severe degrees of necrosis and inflammation were produced by tetracycline, chloramphenicol, and chloramphenicol succinate. The oxytetracycline preparations were less damaging. Referring to previous reports that muscle necrosis and inflammation followed injections of penicillin, streptomycin, tetracycline, beeswax, peanut oil, and sesame oil, Dr. Hanson said that his findings showed that, although there were differences in the degrees of damage produced by various antibiotics, some local damage occurred with all of those studied, and this should be borne in mind in prolonged therapy.

MEDICAL DEFENCE SOCIETIES

MEDICAL DEFENCE UNION

The seventy-fifth annual general meeting of the Medical Defence Union was held in London on October 4. The president, Dr. S. Cochrane Shanks, referred in his address to the recent death of their treasurer, Dr. Henry Robinson, and to the retirement from the council of Dr. James Fenton, who had given long and devoted service to the Union.

Dr. Cochrane Shanks reported that membership of the Union exceeded 47,000 and that during 1959 one out of every 17 members applied for assistance. 390 cases were referred to the solicitors. There were 106 cases of alleged professional negligence. Eleven were fought, and all except one of these were won. Of the remainder, 64 cases were abandoned and 31 were settled by a payment made or shared by the Union. A common cause of action for negligence against surgeons was failure to remove a swab from a patient's body, and in 1959 the Union dealt with 20 such cases. Dr. Cochrane Shanks referred to the recently published annual report of the Medical Defence Union and to the special section therein which set out the surgeon's duty in ensuring that no swabs were left behind. The surgeon must satisfy himself that (in the words of the report) "there is an efficient system in force for counting swabs and that the person on whom this duty falls is familiar with the system and competent to follow it, and that the system has been followed, and, by direct inquiry prior to closing the operation wound, that all the swabs have been accounted for"; and he must himself "take all reasonable precautions to verify that all the swabs have been removed by calling upon his recollection of the number and position of the swabs he has inserted and by making such visual and manual search of the operation field as is possible and is compatible with the safety and welfare of the patient." Dr. Cochrane Shanks concluded his address by thanking the staff of the Union for their devoted service during the year and to the solicitors for all their help and wise counsel.

MEDICAL PROTECTION SOCIETY

The Medical Protection Society held its sixty-eighth annual meeting at its new premises, 50 Hallam Street, on October 5 under the chairmanship of Dr. F. Harwood Stevenson.

In presenting the annual report of the council Dr. Stevenson paid tribute to the late Sir Ernest Rock Carling, who had been president of the Society since 1944. A notable event during the year had been the transfer from the Society's former very cramped quarters to the new building in Hallam Street. The Society's financial reserves now stood at over £270,000, and with a membership of 36,000 and an excess of £17,000 in income over expenditure during the year there was no intention at this time of raising the annual subscription over the present £2. The chairman then made the usual reference to certain causes of cases the Society had had to deal with during the year—in particular, leakage of thiopentone during or after injection, radial-nerve palsy after intramuscular injections into the upper arm, and the special hazard of sepsis after hydrocortisone injections. He also referred to the first—and successful—appeal to the Judicial Committee of the Privy Council* against a decision of the General Dental Council to erase a member's name from the *Register*. This, he said, had drawn from the Judicial Council a definition of certain aspects of what might be held to be infamous conduct in a professional respect. The treasurer, Mr. W. M. Mollison, then presented the annual financial statement.

The annual report follows the usual pattern. It includes a picture of the Society's new house and a reproduction of the portrait of Sir Ernest Rock Carling which the council commissioned shortly before his death. Among the medical cases of particular interest is that of a woman who suffered from prolonged discoloration of her skin after a course of intramuscular iron injections into the deltoid. The fact that the makers of the iron preparation in question gave detailed directions with each set of ampoules that the injection should be injected only into the gluteal muscles and that special care was necessary to avoid leakage along the needle track had made this case virtually impossible to defend. A settlement had therefore had to be arranged.

*See *Brit. med. J.*, 1960, **1**, 1819.

Nova et Vetera

THE JARDIN DU ROI: SEEDBED OF SCIENCE

The Jardin du Roi was a real seedbed of science. Though it began as a botanical garden, and reverted to the title of Jardin des Plantes, it was for a century and a half "le grand foyer scientifique de l'Europe."

It was an offshoot of a botanical garden established in Paris in 1597, where doctors could obtain a grounding in botany. Here Guy de la Brosse (d. 1641) worked until the school of medicine in Paris built an anatomical theatre in this garden. So he moved the Crown to establish another garden under the royal physician. Though the idea was approved in 1626, it was not until 1635 that the property was formally occupied: a house surrounded by a garden of 24 arpents, or 36 acres (Clos de Coypeaux), on the left bank of the Bièvre. Under Charles Bouvard (1572–1658) its nominal superintendent, Guy de la Brosse, worked to establish it with a full complement of 2,000 plants.[1] Bouvard, a professor at the Collège de France and first doctor to the king, set the tradition whereby that office was associated with the superintendency of the garden. He seems to have been a tartar, for his *Historiae hodiernae medicinae veritatis* (c. 1635) contained strong criticisms of the medical practice of his day.

Before the death of Guy de la Brosse in 1641, rooms were opened for the teaching of botany, chemistry, and

astronomy, and it was renamed the Jardin du Roi. His nephew, Guy-Crescent Fagon (1638–1718), was appointed professor of botany in 1664, and carried on the work of stocking the garden by travels in the Auvergne, the Alps, and the Pyrenees (reflected in his *Hortus Regius*), virtually doubling the number of plants. In 1683 Fagon secured the appointment of J. P. de Tournefort (1656–1708), who travelled even further: to England, Holland, and later to the Levant and Africa. Tournefort's book, *Les Éléments de Botanique* (1694), followed his appointment as member of the Académie des Sciences.

The first professor of chemistry was a Scotsman, William Davisson. Appointed Intendant of the Jardin du Roi in 1647, he opened a course in chemistry a year later. His reputation as author of *Philosophia pyrotechnica seu cursus chymiatricus . . .* (Paris, 1640) and his reputation at the Jardin led Sir Thomas Urquhart to write of him in 1652: "The excellency of Doctor William Davisson in Alchemy, above all the men now living in the world, whereof by his wonderful experiments he giveth daily proof although his learned books published in the native tongue did not evidence it, menteth well to have his name recorded in this place and after him."[2] Davisson had left two years earlier to become physician to the King of Poland.

His successor as professor of botany and chemistry at the Jardin from 1651 to 1664 was Nicasius le Fèvre (d. 1669). He attracted a considerable audience, including John Evelyn (1620–1706), the diarist, who had heard him in 1647 and later described him as "my Master in Paris." Evelyn and Sir Kenelm Digby, together with "divers Curious Persons of Learning and quality," attended his "first opening the course and preliminaries, in order to operation."[3] Le Fèvre's *Traité de la Chymie* (1660), a two-volume summary of his teaching, was translated into German and into English three times (in 1662, 1664, and 1670). He was appointed chemist to King Charles II, and apothecary to the household, and became an Original Fellow of the Royal Society of London. Le Fèvre was entrusted with the Laboratory at St. James's Palace (c. 1664–6).[4] In England he wrote avowedly for the apothecaries, and must have contributed greatly to the use of chemical as opposed to botanical remedies in their practice.

Le Fèvre's successor at the Jardin was Christoph Glaser, of Basle, who published a *Traité de la Chymie* (1663) which was also translated into English and German. He suffered a brief term of imprisonment in the Bastille in 1676 for suspected complicity in some poisoning cases and died in 1678 soon after his release. Glaser's pupil (who disliked him) was Nicholas Lemery (1645–1715), who went to England before graduating at Caen in 1693. In his *Cours de Chymie* (1675) he set the tone not only of chemistry taught in the Jardin but of that taught elsewhere.[5] It was one of the earliest based on experimental work which he had carried out in a laboratory, and passed through a dozen editions in his lifetime, as well as being translated into Latin, English, German, Italian, and Spanish. The *Philosophical Transactions* (xii, 1683–4) remarked of the fifth edition: "It is of such reputation in the world that notice of additions to it can't be thought ungrateful to the reader." Not the least value of this work is the fact that it publicized the first inorganic catalytic process to come into general use: the manufacture of sulphuric acid by burning brimstone with nitre. The nitrous oxides from the nitre carried on the reaction from SO_2 to SO_4.[6]

The heyday of the Jardin du Roi is, however, traditionally associated with that singular scientific dynasty the Jussieu family. Beginning with Antoine Jussieu (1686–1758), who succeeded Tournefort as director in 1708, the family was active in the Jardin for the rest of the century. His brother Bernard (1699–1777) edited Tournefort's book, refined Linnaeus's sexual classification of plants, introduced the famous cedar of Lebanon into the Jardin, and explored the potentialities of the coffee bean. A third brother, Joseph (1704–1779), introduced heliotrope and added to his medical abilities those of an engineer. A nephew, Antoine-Laurent de Jussieu (1748–1836), also a professor at the Jardin, published *Genera Plantarum* in 1774, which carried the evolutionary idea perceptively forward, and became in 1808 a member of the Council of the Napoleonic University. Antoine Laurent's son André (1797–1853) carried this remarkable intellectual dynasty up to the nineteenth century.

The Jardin grew with them. They built hothouses, an amphitheatre, and laboratories. Its titular connexion with the office of the king's physician was severed. Perhaps its greatest superintendent was G. L. Leclerc du Buffon, who took office in 1739. A bold, imaginative writer, as well as a great administrator, his output was prodigious. By acquisitions and successful enlargement the Jardin spread down to the Seine. Buffon vacated his apartments to make room for further collections. He himself did much to marry the knowledge of astronomers and mathematicians to the facts of the earlier history. His thirty-six-volume history of the earth made its story perceptibly clearer, and did much to forward the idea of modification of the species.

Growth in the Jardin extended to the laboratory. Lemery's successor, E. A. Geoffroy (1672–1731), had a demonstrator, G. F. Rouelle (1703–1770), who in the period 1742 to 1765 proved himself a brilliant investigator. Rouelle was the first to recognize that salts were produced by the combination of acids and bases. (His brother, H. M. Rouelle, isolated urea from urine.) He was credited with the discovery of sulphuretted hydrogen and other compounds. He was also a stimulating teacher, attracting among others Antoine-Laurent Lavoisier,[7] Proust, and Cadet. Diderot admired him and came to his lectures.

Two of Rouelle's pupils, B. G. Sage (1740–1824) and P. J. Macquer (1718–1784) were themselves innovators. B. G. Sage, who was also Rouelle's successor (in 1768), was passionately interested in meteorological chemistry, and 10 years later he established a chair of mineralogical chemistry at the mineralogical museum where Rome de l'Isle and F. A. Chaptal were trained. In 1783 Sage went on to persuade the government to establish the École des Mines. The second innovator, P. J. Macquer, was one of the first to regard chemistry as a science apart from its use to pharmacy and the arts.[8] For the arts, especially dyeing and porcelain, had for some time involved professors of chemistry at the Jardin. Indeed, a regular constellation of talent clustered round the new chairs that were set up in the Jardin during the eighteenth century. L. J. M. Daubenton, A. F. de Fourcroy, Vicq d'Azyr,[9] and Portal all lectured to the public. But when Buffon died in 1788 and his successor, La Billarderie, took over, the Jardin du Roi had reached the apogee of its greatness. Four years later La Billarderie emigrated and was replaced by Bernardin de St. Pierre, who presided over its metamorphosis into a Museum of Natural History.

W. H. G. ARMYTAGE.

---

[1] Agnes Arber: "The Botanical Philosophy of Guy de la Brosse," *Isis*, 1913, **1**, 359–369.

[2] E. T. Hamy: "William Davisson," *Nouvelles Archives*, Série 3 X (Paris, Muséum d'Histoire Naturelle), 1898, 1–38, *D.N.B.*

[3] E. S. de Bier: *The Diary of John Evelyn* (Oxford, 1955), **3**, 336; **3**, 49.

[4] His English laboratory contained the Cabinet of Drugs which had belonged to the wife of Oliver Cromwell; R. T. Gunter: *Early Science in Oxford*, **1**, 39 (1923).

[5] Jean Paul Contant: *L'Enseignement de la Chimie au Jardin royal des Plantes de Paris* (Cahors, 1952).

[6] Lynn Thorndike: *A History of Magic and Experimental Science* (New York, 1958), **8**, 146–153.

[7] Henry Guerlac ("A note on Lavoisier's scientific education." *Isis*, 1956, **47**, 211–216) suggests that Lavoisier actually worked with Rouelle at his house and apothecary's shop on the corner of the Rue Jacob and the Rue des Anges, in the St. Germain quarter.

[8] L. J. M. Coleby: *The Chemical Studies of P. J. Macquer* (1938).

[9] He was secretary of the Royal Society of Medicine, founded in 1776, which kept in touch with provincial physicians, learning of the maladies in their areas, and dispatching directions and medicaments for coping with them. It had a journal, organized meetings of physicians and surgeons, and published prize essays.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Bendrofluazide

"Aprinox" (Boots).
"Centyl" (Leo).
"Neo-Naclex" (Glaxo).

Chemistry.—Bendrofluazide is 3-benzyl-6-trifluoromethyl-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, and is an analogue of chlorothiazide, being the 3-benzyl derivative of hydroflumethiazide.

Pharmacology.—The essential action of bendrofluazide is the same as chlorothiazide and hydrochlorothiazide, but it is on a weight basis more potent, 10 mg. being equivalent to about 1 g. chlorothiazide. However, bendrofluazide has a more prolonged action which may last about 18 hours as compared with the 12-hour diuresis usually induced by chlorothiazide and hydrochlorothiazide. This longer action is not necessarily an advantage when it interferes with the patient's sleep at night.

Bendrofluazide increases the urinary excretion of sodium and chloride in almost equimolar amounts, and the resultant loss of these ions is accompanied by increased elimination of water. The excretion of potassium is also increased, particularly when treatment is prolonged, sodium chloride intake is restricted, and there is increased adrenal secretion of aldosterone. There is little inhibition of carbonic anhydrase.

Therapy.—Bendrofluazide is used in the relief of oedema from any cause, and also as an adjuvant to hypotensive agents. In oedema the initial dose, depending on the severity of the oedema and its cause, is 5–10 mg. daily or on alternate days. Subsequently 5–10 mg. is required intermittently in accordance with clinical response. To enhance the action of hypotensive drugs 2.5–5 mg. is required daily.

There is no convincing evidence in clinical practice that any one member of benzothiazide compounds is more effective than another or gives rise to significantly less potassium loss.

Side-effects.—Prolonged or continuous treatment of a patient whose oedema does not respond may induce depletion of potassium, leading to increased sensitivity to digitalis in cardiac failure and to psychiatric disturbances and coma in hepatic cirrhosis. Supplements of potassium chloride should therefore be given in refractory cases requiring prolonged treatment.

N.H.S. Basic Price.—2.5-mg. tabs., 100 for 11s. 2d.; 5-mg. tabs., 100 for 19s. 3d.

"Ophthalmia neonatorum was reported as causing 28% of the blindness in a sample group of children in schools for the blind in 1907. But by 1954–5 the proportion of ophthalmia neonatorum cases among new pupils entering schools for the blind had dropped to 0.1%. Progress against blindness due to syphilis has been nearly as good. In 1940 an estimated 7.9% of all legal blindness in the U.S. was due to this disease, but by 1957 the percentage was down to 3.8, and among the newly blind in that year it accounted for only 2.0% of all cases. Among school-age children the percentage of all cases of blindness caused by syphilis dropped from 5.2 in 1933–4 to 1.4 in 1954–5, while among new pupils in the latter year the figure was 0.6%." (*Progress in Health Services*, issued by the Health Information Foundation, U.S.A., September, 1960.)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Statistics of Road Accidents

SIR,—In the light of the report of the British Medical Association Committee on the above subject (see *Journal*, January 23, p. 269), supplemented by the Road Research Laboratory's report on the Christmas road deaths,[1] is it not time that the official statistics on road accidents (which are widely quoted as authoritative) should be brought into line with the facts of the situation?

The Ministry of Transport's official publication, *Road Accidents*,[2] grossly underestimates the number of accidents due to drinking. This is the opinion of the B.M.A. Committee and (as I think) of all others who have impartially studied the subject. In the case of fatal accidents, a police report, often completed *before* the inquest, is sent to the Statistical Department of the Ministry, and so helps to erect a statistical survey on insecure foundations. The notes of evidence, taken on oath at the inquest, would supply a more correct version of what really happened.

The Registrar-General's *Statistical Review*[3] records that over 20,000 deaths per annum result from "accidents, poisoning, and violence," and has a column headed "causes of death." Yet in not one of these 20,000 deaths is alcohol ever mentioned or even hinted at as a causative factor, except in the few odd cases of acute alcoholic poisoning. These misleading figures are the result of the incomplete data afforded by coroners' certificates. These could be amended so as to indicate, not only the type of injury and the part of the body injured, but also any "antecedent causes," or "other conditions contributing to the death," such as are provided for in an ordinary certificate of death in medical cases.

I am informed that Part V of a coroner's certificate (which is applicable to accidental deaths) is sent weekly to the Statistical Department of the Registry at Southport; and that the form including Parts I–IV is sent periodically to the Medical Department of the Registry at Somerset House. I suggest that one or other (or both) of these documents should have space for the above details and also for the wording of the verdict at the inquest and for any rider attached thereto. This might involve some extra expense, but the information obtained would be invaluable and I think surprising. In the case of the (comparatively few) deaths due to railway accidents, coroners are required to send to the Ministry of Transport another certificate in which a space is reserved for the above details. Why should not the same procedure be adopted in the case of road deaths?

At present there are many fatal accidents in which drink is known to be involved, but in which this important contributory factor is never recorded except in coroners' records. Also, in most serious road accidents not resulting in a death, the injured are taken to hospital and so escape examination for intoxication. And I strongly suspect that many slightly injured persons, who know that they have been indulging, make the most of their symptoms in order to be taken at once to hospital and escape examination by the police surgeon. Thousands of inquest reports are stored away in coroners' offices, in town halls, and elsewhere, and, after looking through hundreds of these, one is impressed by the mass of relevant information about fatal accidents of all kinds which is at present being absolutely wasted.

I am informed by the General Register Office that the classification of deaths must conform to an internationally agreed practice, in which normally only one

"cause" is shown for each death. But in the case of accidental deaths there is already a dual classification, which complicates matters, and the Registrar-General does not think that he would be justified in endeavouring to get further details from coroners. But there is a medical advisory committee on nomenclature which gives "advice and assistance" to the Registrar-General. I suggest that this committee should endeavour to bring the official statistics of accidental deaths (which were designed for a horse and railway era) into line with the realities of a motoring age. The word "cause," as used over many pages of the *Statistical Review*, should be clearly defined and qualified so as to prevent its being used as a cloak to gloss over the personal factor which underlies nearly every accident, as has been so clearly brought out in the reports of the B.M.A. and of the Road Research Laboratory. I may say that I have been able to draw on the experience of a London coroner in making the above suggestions.—I am, etc.,

Leicester. N. I. Spriggs.

References

1 *Road Accidents—Christmas 1959*, 1960. Road Research Technical Paper No. 49. H.M.S.O., London.
2 Ministry of Transport, *Road Accidents, 1958*, 1959. H.M.S.O., London.
3 *Registrar-General's Statistical Review of England and Wales for 1958, Part I*, 1960. H.M.S.O., London

Child Psychiatry

Sir,—The trouble with child guidance clinics is not just the lack of staff but the wastage of psychiatric time in the ritualistic approach that pertains in these clinics. If the case is "seen by the doctor" it must also be fully investigated by the psychiatric social worker and the psychologist in such a way that both mother and child are interrogated by at least two people; this is as unnecessary and cumbersome as a medical patient and relative being submitted to a full physical investigation, *x*-rays of the whole skeleton, and an almoner's inquiry. Then, too, each case must be discussed fully in a further time-taking conference which is justifiable only in a teaching institution. The practice, however, continues in order to satisfy the status-conscious psychologist and social worker, who have no experience of the satisfactory team-work that is going on daily in hospitals, often with little personal contact between the members of the team.

The situation does not prevail in hospital clinics. In my own hospital there is no waiting-list, for new patients may come without appointment on a certain day. Working on ordinary medical principles the new case is examined by the psychiatrist, who asks for such further examinations as may be necessary, and makes a diagnosis according to the facts put before him. On these lines 360 cases were dealt with in one year by one psychiatrist, which is a considerable improvement on the usual numbers in a child guidance clinic, where the whole-time psychiatrist may see at the most three new cases a week.

It is perhaps not fully realized that the child guidance service is the only field where the other members of the "team" have not received their preliminary training in a general hospital. The psychiatrist not only must have considerable clinical acumen, but also be something of a politician to maintain any equilibrium. This also is the only consultant service not dominated by the Ministry of Health. In the opinion of many, child guidance clinics should be reserved for the ascertainment and treatment of educational problems, and that the child psychiatrist should be transferred into a hospital situation, but this has been overruled by the Ministry of Education. General practitioners could help by taking an interest in the facilities in their area, patronizing hospital clinics and favouring these with personal contact (which would be most welcomed by the psychiatrist), and urging that clinics be established in a hospital setting as are all other consultant services.—I am, etc.,

Selly Oak Hospital, Birmingham 29. Louise F. W. Eickhoff.

Faulty Anaesthetic Apparatus

Sir,—Dr. P. Ayre's letter (October 8, p. 1084) serves to stress the all too frequent fallacy in the teaching of dental anaesthesia—namely, that the percentage oxygen indicated by the anaesthetic machine is in fact an accurate one. The assumption in Dr. Ayre's case that on previous occasions the machine had always delivered 10% when set to this figure on the regulator is clearly false, since respiration of a 90% nitrous-oxide and a 10% oxygen mixture results, in normal individuals, in marked cyanosis. Machines of the type to which Dr. Ayre no doubt refers can usually be relied upon to deliver an oxygen percentage *greater* than that indicated by the regulator, and the probability is that following servicing the machine became more and not less accurate.

I have met the same unexpected and frightening emergency as Dr. Ayre, and I can sympathize with him, but I feel that stress should be laid upon the fact that *no* indicated percentage should be relied upon during dental anaesthesia and that the patient's colour should be the sole guide as to oxygenation.[1]—I am, etc.,

The Queen Elizabeth Hospital, Birmingham 15. J. McNaught Inglis.

Reference

1 Inglis, J. McN., and Campkin, V., *Brit. dent. J.*, 1960, **108**, 351.

Sir,—I would like to express my agreement with the views put forward by Dr. Philip Ayre (October 8, p. 1084). Dr. J. G. Bourne in his recent book *Nitrous Oxide in Dentistry*[1] has drawn attention to the discrepancies in oxygen percentage as delivered by intermittent positive-pressure machines in use for dental anaesthesia.

The other matter—that of the servicing of anaesthetic apparatus—is one which demands vigilance on the part of anaesthetists. Some years ago, in the early days of the National Health Service, the group secretary of a peripheral hospital group made a serious proposal, doubtless with a view to economy, that the anaesthetic apparatus in use in the group should be serviced by a mechanic on the engineering staff of the main hospital in the group: these engineering employees have had no training in the working of anaesthetic apparatus, and would, of course, be quite incompetent to carry out such services. This ridiculous proposal was quickly scotched, and the servicing of anaesthetic apparatus continues to be done by the engineers of the manufacturers.

In order that neither the hospital group nor the lay official mentioned may be identified, I beg leave to sign myself with the motto of the Association of Anaesthetists of Great Britain and Ireland.—I am, etc.,

In Somno Securitas.

Reference

1 Bourne, J. G., *Nitrous Oxide in Dentistry: Its Dangers and Alternatives*, 1960. Lloyd-Luke (Medical Books), London.

Gangrene from Thiopentone

SIR,—I certainly misread the paper[1] by Professor J. B. Kinmonth and Mr. R. C. Shepherd as they say (September 24, p. 939) On their part they have not interpreted my work (with Dr. D. B. McDougal) correctly (see August 6, p. 414). What we found was that, if reserpine was given to mice beforehand to remove the store of noradrenaline, the injection of thiopentone caused necrosis and ulceration in a very much smaller proportion of mice, and delayed the occurrence of gangrene. Our conclusion was that thiopentone appears to cause gangrene because of the local release of noradrenaline. We do not, however, regard the effect of this local release as due to a "transient vasoconstriction."

The work I have done with my colleague, M. J. Rand,[2 3] shows that tissues which have a sympathetic innervation can take up noradrenaline from the blood-stream and hold it in a store from which it can be released by various substances. Our knowledge of the physiology of this stored noradrenaline has only just begun, and the stages by which its release leads to gangrene are at present unknown.—I am, etc.,

J. H. BURN.

School of Medicine,
Washington University,
Saint Louis, U.S.A.

REFERENCES

1 Kinmonth, J. B., and Shepherd, R. C., *Brit. med. J.*, 1959, **2**, 914.
2 Burn, J. H., and Rand, M. J., ibid., 1958, **1**, 903.
3 —— —— *J. Physiol.*, 1958, **144**, 314.

Megimated Barbiturates

SIR,—The medical memorandum by Drs. B. W. McGuinness and F. J. Roberts (October 1, p. 996) has renewed my interest in this complex and controversial subject. I have previously suggested in your correspondence columns (November 21, 1959, p. 1096) that widespread use of megimated barbiturates might reduce the incidence of death from barbiturate poisoning. The reported death caused by ingestion of a large number of "phenaglate" capsules (quinalbarbitone sodium 50 mg., phenobarbitone 25 mg., bemegride 7.5 mg.) need not destroy faith in "mylomide" tablets (amylobarbitone 100 mg., bemegride 10 mg.). Frommeyer[1] believes that barbiturate antagonists have not enhanced the beneficial results of therapy of acute barbiturate poisoning whereas British opinion supports the value of bemegride.[2–4]

A trial of prolonged narcosis therapy modified with megimated barbiturates has been carried out at a psychiatric hospital. The work followed that of Gershon and Shaw[5] and of Trautner *et al.*[6] Four specially compounded tablets (amylobarbitone 250 mg., bemegride 25 mg.) were given at 8 a.m., 2 p.m., and 8 p.m. This was supplemented alternately with paraldehyde or unmodified amylobarbitone sodium to ensure sleep. It was not a controlled trial, merely a try-out for clinical impressions of usefulness and safety. Fourteen female cases were included, with ages ranging from 19 to 52 years, and up to February, 1959, a total of 16 treatments were given. With one exception, they were all in one closed admission/observation ward, and the number of days of treatment varied from 10 to 28. In the 16 treatments mentioned, the patients' sleep never deepened to danger-point. Two preventable side-effects occurred. First, deep-vein thrombosis, before daily prophylactic physiotherapy was used, and, second, in the case treated in a different ward with different nursing staff treatment was suddenly withdrawn on day 10 and the patient had barbiturate-withdrawal convulsions.

In spite of what follows I think this is a safe method of giving continuous narcosis therapy, but much depends upon staff, and continual observation of the patient. After February, 1959, the patient in another ward who had barbiturate-withdrawal fits was given a second narcosis modified by megimated barbiturates. On day 14 she died in the night. It was presumed that she died of asphyxia in a fit, and the post-mortem findings were consistent with that diagnosis. She was then noted to have had epileptic fits before her first narcosis therapy. Great caution is required in persons subject to epilepsy. The more bemegride-barbiturate mixture swallowed, the greater the relative effect of the bemegride, so that, rather than going into coma, the patient is more likely to have a convulsion.

I have used this therapy only once since February, 1959 in a male admission unit at another psychiatric hospital. The patient was a 31-year-old with a severe obsessive-compulsive neurosis. Although narcosis therapy did not help his anxiety or tension, it was conducted with complete safety.

In conclusion, from experience in giving large doses of a bemegride-barbiturate mixture (3 g. of amylobarbitone mixed with 10% bemegride in divided doses daily for ten days or more), and from experience in the treatment of acute barbiturate poisoning using bemegride, I am convinced that the drug works in clinical practice. I shall therefore continue to prescribe mylomide in preference to unmodified amylobarbitone under certain circumstances. I have never prescribed phenaglate and would not miss it if it were withdrawn.—I am, etc.,

R. NEVILLE.

Hellingly Hospital,
Hailsham, Sussex

REFERENCES

1 Frommeyer, W. B., in Conn, H. F., *Current Therapy 1960*, 1960, p. 682. Saunders, Philadelphia.
2 MacLean, K., *Medical Treatment*, 1957, p. 582. Churchill, London.
3 Dunlop, D. M., Davidson, S., and Alstead, S., *Textbook of Medical Treatment*, 1958, 7th ed., p. 851. Livingstone, Edinburgh.
4 *British National Formulary, 1960*, Alternative Edition, 1960, pp. 168 and 222. B.M.A. and Pharmaceutical Society of Great Britain, London.
5 Gershon, S., and Shaw, F. H., *Brit. med. J.*, 1957, **2**, 1509.
6 Trautner, E. M., Murray, T. W., and Noack, C. H., ibid., 1957, **2**, 1514.

Phenothiazine Derivatives

SIR,—I was interested to read the letter by Dr. R. F. O'Donoghue (October 1, p. 1022) regarding the use of a phenothiazine derivative—promazine hydrochloride—as an adjunct to analgesia in labour, and I fully agree that promazine hydrochloride, and for that matter other phenothiazines, have a marked anti-emetic and analgesic potentiating effect in labour. I would like to describe my experience with promazine in the more troublesome forms of nausea and vomiting during pregnancy.

Sickness in pregnancy is extremely common in the first three or four months, although it is not quite so frequently noted in the early morning as the classical literature would lead us to believe. In the vast majority of cases it is mild and responds to reassurance with some sensible rearrangement of the pattern of meals, but others continue and require further treatment. Many courses are open, including antacids, antihistamines, mild anti-emetics, such as "avomine" (promethazine chlorotheophyllinate) or one of the proprietary preparations combining these with pyridoxine. This type of symptomatic therapy controls a further percentage, but the occasional case progresses despite such measures, and, if uncontrolled, becomes a case of hyperemesis gravidarum. Whereas an "uncontrolled" case had not

been seen for a number of years, four such cases have occurred in this practice in the last year, and, although some may criticize the classification of hyperemesis gravidarum *per se*, they certainly needed more dramatic treatment than the measures outlined above. The logical choice was the phenothiazines, because of their marked anti-emetic action, and "sparine" (promazine hydrochloride) was selected as it had been reported as one of the less toxic members of this group of drugs.[1]

The first patient, aged 35, was in her second pregnancy and failed to stop vomiting with bed-rest, dietary advice, and promethazine tablets. She progressed to the stage of being unable to keep down any food or fluids and was immediately controlled with promazine 50 mg. by intramuscular injection. This was maintained by tablet medication and she had no further trouble.

A second patient also resisted routine treatment and was unable to keep solids or fluids down for a few days. Promazine, 25 mg. four times daily by mouth, was sufficient to control her nausea and vomiting, but the treatment had to be continued until the end of the pregnancy as otherwise she promptly relapsed.

The third patient was slower to call medical attention and had progressed to dehydration with acetone in the breath and urine and some clinical signs of icterus due to hyperemesis. Promazine, 50 mg. intramuscularly, was given eight-hourly for the first 24 hours, and the improvement was so marked that tablets were substituted which maintained the control. An attempt was made later to discontinue the drug, but a further exacerbation of severe vomiting occurred necessitating further parenteral followed by oral promazine. The tablets were continued to the end of the pregnancy and no more vomiting took place, although there was occasional nausea, suggesting that 25 mg. t.d.s. was perhaps too small a dose for such a severe case.

In a fourth patient vomiting was progressive and was not controlled by the usual dose of intramuscular promazine, although she later settled down in hospital with sedatives and parenteral fluids.

As no other drug was used in conjunction with promazine the overall impression gained was that promazine has powerful anti-emetic and sedative qualities, and can save sending the more severe types of vomiting in pregnancy to hospital.—I am, etc.,

Surbiton, Surrey. T. J. C. WARRINER.

REFERENCE

[1] May, A. R., *Brit. J. clin. Pract.*, 1958, **12**, 348.

Congenital Talipes

SIR,—I was very interested to read Mr. W. A. Crabbe's article concerning the aetiology of congenital talipes (October 8, p. 1060). In a series of 20 cases of talipes equino-varus seen between 1952 and 1959 in Indian children in Mysore City, South India, I found associated anomalies in six cases, an incidence of 30%. After excluding the case of meningomyelocele the figure becomes 25%. The anomalies were as follows: claw hand, 1; absent rectum and mongolism, 1; imperforate anus, 1; harelip, 1; absent nails and webbed digits, 1; and meningomyelocele, 1. In the case associated with absent nails and webbed digits and in one other case without associated anomalies there was a family history of talipes. In two other cases without associated anomalies siblings had imperforate anus and hypospadias respectively.

This is a small series but may be of some interest to any who are studying congenital defects.—I am, etc.,

Hayling Island, Hants. D. E. MARGARET PIERCE.

Bastard Dosage

SIR,—I would like to congratulate the Joint Anglo-American Working Parties on their report on "Evolution of Rheumatic Heart Disease in Children" (October 8, p. 1033), which warrants very careful study. I would, however, draw your attention to one blemish which I was surprised to find in the report after reading through the list of the names of the eminent contributors. The blemish is to use a "bastard" dosage scale—that is, in the paragraph "Comparison of Treatments" it states, "*Aspirin*—a daily dosage of 60 mg. per pound of body weight . . ." Surely this should have been expressed as 1 grain per pound of body weight (120 mg. per kilogramme).

I appreciate at the present time in this country there are two systems of measurement of dosage, but why introduce a "mixed grill"? Most hospital doctors are steadily dropping the apothecaries system with its confusing symbols and using the metric system largely. In some medical schools only the metric system is being taught, so it was somewhat of a shock to find in a paper of international status the emergence of a third system.—I am, etc.,

Nottingham. A. P. M. PAGE.

Estimation of Faecal Fat

SIR,—The paper of Dr. B. D. Pimparkar and his associates (September 24, p. 894) on the correlation of radioactive and chemical faecal fat in different malabsorption syndromes will be of great interest to those who have worked in this field. There have been suggestions in the past[1 2] that patients may be seen who have steatorrhoea detectable by chemical fat estimation but no increase in faecal ^{131}I triolein excretion—i.e., false negatives for the triolein test. I have seen no previous reports of false positives. It is generally felt[3 4] that a faecal excretion of 6 g. of fatty acid per day on a normal ward diet indicates malabsorption, and if total lipids are measured the figure of 7 g. per day is more appropriate.[5 6]

A personal study has been carried out on a group of 55 hospital in-patients, eating a normal ward diet, about one-third of whom had malabsorption of fat as judged by estimation of faecal total lipids. Faecal radioactivity after ingestion of ^{131}I triolein in 10 g. of peanut oil has been compared with faecal total lipids in 59 tests in the above patients. Using 7% of the ingested dose in the stools, and 7 g. of total lipids per day in the stools as the upper limits of normal for the two parameters, disagreement was found in 11 tests. There were two false positives (3.6%) and nine false negatives (15.8%) for the triolein test when compared with faecal lipids. However, if a faecal excretion of radioactivity below 3% was considered normal and above 7% abnormal and between these values it was considered equivocal and the point settled by faecal lipid determination, there were only five false negatives (8.5%). It is my practice to consider readings between 3–7% indeterminate with the object of reducing the false negatives. This confirms the observation of Pimparkar and his colleagues that false negatives are commoner than false positives. It is a pity that we do not know the explanation for these false negatives, and they may repay further study.

In one of the false negatives in the present series, a patient with entero-colitis in whom several raised faecal lipid estimations contrasted with normal faecal radioactivity on two occasions, an attempt was made to demonstrate fat synthesis in culture by faecal

bacteria, and later by culture of jejunal and ileal contents obtained at laparotomy, using the method of Frazer.[7] These were unsuccessful. It may be that the difference in absorption of ^{131}I triolein from ^{14}C triolein shown by Van Handel and Zilversmit[8] explains most cases, and that we do not need to invoke possible fat excretions as a mechanism.

Determinations of plasma radioactivity were made in only about half of the patients in this study, but the results suggested that only in very gross steatorrhoea was there a good and certain inverse correlation with faecal lipid levels. Dr. Pimparkar and his colleagues are to be congratulated on pointing out the shortcomings of the triolein test and for having produced the first large series of parallel faecal fat and radioactivity estimations.—I am, etc.,

St. Thomas's Hospital, London S.E.1. R. VAUGHAN JONES.

REFERENCES

1 Lubran, M., and Pearson, J. D., *J. clin. Path.*, 1958, **11**, 165.
2 Mohamed, S. D., and Hume, R., ibid., 1959, **12**, 535.
3 Cooke, W. T., *Brit. med. J.*, 1958, **2**, 261.
4 Jones, F. Avery, *Proc. roy. Soc. Med.*, 1959, **52**, 38.
5 Annegers, J. H., Boutwell, J. H., and Ivy, A. C., *Gastroenterology*, 1948, **10**, 486.
6 Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E., ibid., 1947, **9**, 272.
7 Sammons, H. G., and Frazer, A. C., *Clin. Chem.*, 1956, **2**, 272.
8 Van Handel, E., and Zilversmit, D. B., *J. Lab. clin. Med.*, 1958, **52**, 831.

Adiposity

SIR,—I was most interested in your correspondent Dr. L. M. Shirlaw's hypothesis (September 24, p. 946) that adiposity is a vestigial remnant. There is abundant anthropological evidence that this is so. Perhaps the best-known example is the African bushman, a race now practically extinct through annihilation, whose skin was extremely loose and wrinkled so that he was enabled to store fat under it during a good hunting season, when he was reputed to gorge himself to a fantastic extent. The fat was mainly stored in the abdomen and buttocks, and there is an apocryphal old Boer story that a bottle of brandy and glasses could be perched on his posterior. —I am, etc.,

London W.13. JOHN H. SWAN.

Mental Health

SIR,—Professor A. V. Neale's repetition (August 27, p. 664) of Professor W. H. Trethowan's plea "against any further propagation of the absurd 'mind-body dualism' which so strongly colours the thinking of many practitioners and persistently interferes with the adequate appreciation of man as a totality" deserves warm applause from psychiatrists, of whom the majority in this country have been trying to destroy the false concept of dualism for years past.

Unfortunately, not only among the public as a whole but, less excusably, among members of the medical profession also, the dualistic concept persists and underlies the widespread tendency to equate psychiatry with psychoanalysis and to believe that psychiatrists are concerned only with the discovery of the causes of disease and its treatment by dealing with the mind in isolation and that they are almost unaware of the physical basis of disease. In fact, British psychiatrists are (or should be), first of all, physicians with a sound general knowledge of the normal functioning of the body and the many influences, both physical and psychological, which can cause functioning to deviate from normal. They recognize that primarily physical disturbance cannot occur without an accompanying psychological disturbance and similarly that primarily psychological disturbances produce corresponding physical disturbances. It follows that in every patient the psychiatrist gives due consideration to both these aspects, although the presenting symptoms which bring the patient to him appear to be primarily in the sphere of disturbed mental functioning.

When I was a student I was taught that diseases were either organic or functional, and, whether this impression was intended or not, I qualified believing that it was not quite respectable to have a functional disease, and that such patients, together with those who showed signs of more serious mental disease, were not the problem of the general physician but should as quickly as possible be unloaded, as it were, in the psychiatric dustbin. I find it amusing, therefore, to note that, now that through the efforts of psychiatrists themselves psychiatry has become a more or less respectable branch of medicine, take-over bids are being made by other branches of medicine for various aspects of psychiatric care. This seems particularly true in the field of mental subnormality, perhaps the most medically understaffed and lowest in regional board financial priorities of all the specialties.

In recent years, in spite of inadequate establishments, the medical staff of hospitals for the mentally subnormal have struggled on an out-patient and in-patient basis to practise psychiatry in the fullest sense defined above, using in addition to the ordinary methods of clinical examination all the modern special techniques of pathological, biochemical, genetic, and electroencephalographic investigation. They have given the appropriate treatments of specific defects and the modern drug treatments to control the behaviour disorders which accompany mental subnormality of all grades, and whose use has transformed the atmosphere of these hospitals and reduced to a minimum the need for mechanical restraint and seclusion. They have, in addition, conducted the time-consuming case conferences directed towards creating and maintaining the therapeutic community in which many of these patients must inevitably spend the greater part of their lives, and psychotherapy sessions for all those medium- and high-grade patients whose disturbed behaviour cannot be simply accepted as an inevitable consequence of their defect of intelligence. The need for these sessions will expand as these hospitals develop their in-patient and out-patient services for the subnormal and psychopathic groups. As Professor Neale says, parents, teachers, social workers, and doctors (and surely nurses, too) all have a significant place in the mental-health teams. This is obviously as true in mental subnormality as in mental illness. However, there seems a current tendency to suggest that mental subnormality is not primarily a psychiatric problem but a training problem and that general medical practitioners might easily replace psychiatric staff without detriment to patient care. Such a view reflects the outmoded, narrow concept of the psychiatrist to which I have referred and a complete ignorance of the true purpose of a progressive hospital for the mentally subnormal. To adopt this proposal would, I submit, quickly condemn such hospitals to the role of stagnant dumping-grounds comparable to the chronic wards of the old-type mental hospitals, in which patients received little but food and a cursory annual physical examination. It is to be hoped that psychiatrists in their enthusiasm to welcome others into the team do not abandon their overall responsibility for ensuring that the team is working in the very best interests of each patient in hospital.—I am, etc.,

Bristol 8. W. ALAN HEATON-WARD.

School Phobia

Sir,—The school phobic child has been a miniature neurotic long before the onset of his refusal. Usually he reflects a similar condition in his parents. There is a definite genetic factor, but there is also a factor which derives from widespread social changes in attitudes to children, and this, to my mind, is the relevant issue. When children misbehave we still feel it is wrong in the old sense, but we doubt whether it is correct to punish them, in a way that our predecessors did not. In short, we tend to replace summary punishment by disapproval. This means that we are containing hostility towards the child over a period. This makes a predisposed child guilty and anxious, whereas summary punishment tends to clear the air. Furthermore, the child may not altogether perceive the cause for continued disapproval, as continuous mental states are foreign to him. This only increases the guilt. As a result he tends to cling to the disapproving parent to reassure himself that he is, in fact, liked, despite appearances. Thus it is a lack of decisiveness in parental attitudes which leads to clinging and closeness. This and their own indecision further irritate the parents, and so a vicious circle arises.

It will be clear that such a child is sensitive to disapproval—that is, overdependent on the approval of others for feeling worth while. When such a child experiences a setback at school, most commonly as the result of a routine change, all his latent fear of not being approved of is resurrected and an affective state of varying degree grows out of this anxiety about school, and in this state the old need to prove the deeper misgivings false is naturally uppermost: hence separation anxiety. But this is no more than a prominent feature of an affective state and varying in degree with the severity of that state. School is the precipitant, and the fear thereof as a disapproving place is the source of the affective state. Hence, school phobia arises more commonly nowadays because, in addition to genetic reasons, there is a current uncertainty as to what is right and what is wrong in behaviour, of such a degree as to vitiate all decisiveness in management and to produce bewildering fears of not being altogether liked in the child. On the other hand, the parental uneasiness at containing hostility against a child leads to compensatory indulgence, so that alongside their insecurity these children are wilful and intolerant of frustration.—I am, etc.,

St. James's Hospital, Portsmouth. R. T. D. Franklin.

Eradication of Malaria

Sir,—Arising from your leading article entitled "Eradication of Malaria" (April 2, p. 1033), letters by Dr. R. B. Heisch (June 4, p. 1736) and Dr. L. J. Bruce-Chwatt (July 9, p. 150) asserted respectively that the sporozoite or the infant parasite index was valuable, and that this would give an idea about the malaria situation in the region. These are really valuable indices in an endemic region. But although the infant parasite index reflects the malaria situation, it depends more on the transmission season and the date on which the blood slide was taken. On the other hand, such indices give no idea in countries where there is an advanced eradication programme. They will always be zero in such a country despite there still being indigenous or imported cases. Moreover, with combined methods of active and passive case detection, almost all the cases will be discovered in such countries, or only by passive detection in better-organized countries. In that event, should not proved cases of malaria be the criterion ?—I am, etc.,

Adana Malaria Institute, Turkey. C. Gökberk.

Sir,—It was perhaps a little unfortunate that you did not publish my reply to Dr. L. J. Bruce-Chwatt (July 9, p. 150) in full but merely put a sentence out of context in your "Points from Letters" column (July 23, p. 313). I wonder if you would be kind enough to publish this explanation of what I meant when I said the sporozoite rate was a more sensitive index of transmission than the parasite rate. I was, of course, only referring to the Shimba Hills Settlement area, where the sporozoite rate remained quite high after the parasite rate had almost been reduced to nil by drugs. I have heard that Dr. Draper and other experts are rumbling in protest, for in some quite malarious regions the sporozoite rates may be very low when the parasite rate is quite high. India, I believe, is a country where the natural sporozoite rate is very low in the anopheline vectors. I repeat that what I said is only meant to apply to holoendemic areas with naturally high sporozoite rates, where insecticides have not been used and where the parasite rate has been greatly reduced by drugs. At Shimba, even after drugs had knocked out the parasites, the sporozoite rate remained quite high; transmission was going on but was veiled as the people were protected. Presumably the infected mosquitoes were coming from untreated adjacent areas, though even this is not certain. In these circumstances the sporozoite rate was a more sensitive index than the parasite rate.

I have tried to make myself clear, and hope you will publish this letter. Being a dilettante malariologist I will be exposed to the darts of the experts. Curiously enough, they seem loath to discharge them.—I am, etc.,

Division of Insect-borne Diseases, Medical Research Laboratory, Nairobi, Kenya. R. B. Heisch.

Origins of Life

Sir,—As the "member of the audience" referred to in your report of the Symposium on the Biology of Space Travel (October 8, p. 1079) who took part in the discussion on Dr. Harlow Shapley's paper, may I say that I did not deal with "steps between amino-acids and nucleic acids"? My point was that many of those who discuss the possibility of life on other planets, like Dr. Shapley in his paper, are content to go no further than suggest the possible origin of proteins. It is true that amino-acids have been produced experimentally by sending electric discharges through an imitation of the earth's primitive atmosphere. But, necessary as proteins are for life, the basic molecule of life is surely nucleic acid, the stuff of which genes are made, for it appears to act as a template along which the amino-acids line themselves up to produce precisely the proteins required for life. The spontaneous generation of a nucleic-acid molecule large enough and of the correct structure needed to serve as a basis for life is a far more difficult thing to explain than the origin of proteins.—I am, etc.,

Dunstable. Alan E. Slater.

Fate of the Claudicator

Sir,—Dr. Shyamal Kumar Sen's suspicions (September 24, p. 940) are unwarranted. None of the patients whose progress was followed in our survey required investigation for renal-artery stenosis. Incidentally auscultation of the aortic and renal areas is part of our routine clinical examination of such patients.[1] In this group of patients with aorto-iliac atheroma, 25 aortograms were available, and, of these, six demonstrated the renal arteries clearly. None, however, showed any evidence of stenosis.—I am, etc.,

St. Mary's Hospital, London W.2. A. Singer.

Reference

[1] Peart, W. S., and Rob, C. G., *Lancet*, 1960, **2**, 219.

Our Hospitals

Sir,—Sir Allen Daley's article in your Special Hospital Number "British Hospitals as They Were Before 1948" (September 10, p. 758) should surely have been named "British Municipal Hospitals as They Were Before 1948," because there is a remarkable bias towards local authority achievement, and that of the voluntary hospitals is brushed off as if it were of little significance. The following statistics of voluntary hospital work over the 50 years before the Health Act[1] may redress the balance: The total income amounted to £490m. 39 million in-patients were treated. 210 million out-patients were dealt with. In 1948 there were 1,100 voluntary hospitals providing 100,000 beds.—I am, etc.,

E. J. R. Burrough,
Administrator,
Oxford. The Radcliffe Infirmary.

Reference

[1] *Hospitals Year Book 1948*, 1948. British Hospitals Association, London.

Subluxation of Sternoclavicular Joint

Sir,—Mr. J. G. Bonnin's article "Spontaneous Subluxation of the Sternoclavicular Joint" (July 23, p. 274) describes only forward displacements of the clavicle. He might be interested in the following further cause of inequality of the prominences of the sternal ends of the clavicles.

A healthy male now aged 25 first noticed, at the age of 17, slight pain in the right sternoclavicular joint and disappearance of the previously present normal prominence there. He felt it might have been caused by his habit of carrying a heavy haversack slung across his right shoulder. On palpation the anterior surface of the prominence has receded to the plane of the manubrium, and its upper surface is lower than on the opposite side—that is, the clavicle is displaced backwards and slightly downwards behind the manubrium. The condition is symptomless. His mother has the dental anomaly of only one pair of upper incisors, and her dentist had told her that this is sometimes associated with congenital absence of the clavicles.—I am, etc.,

Kingsford, New South Wales, Australia. R. G. Williams.

Marksmanship and Crossed Laterality

Sir,—It seems that one cause of bad game shooting, which is not as widely recognized as it might be, is due to crossed laterality. One is always taught to shoot keeping both eyes open. There are many people, however, who are right-handed and yet have a dominant left eye, and *vice versa*. Under these conditions shooting in the normal way is impossible. It also seems very common for right-handed people, who have done a lot of work with a microscope, to develop a dominant left eye. It is a simple matter to determine if an individual has a dominant eye. If this differ from his handedness, he should shoot with one eye closed. This is not in any way incompatible with good shooting.—I am, etc.,

Ipswich and East Suffolk Hospital, Ipswich. B. S. Phillips.

Lumps in the Breast

Sir,—The very alarming state of affairs revealed by Drs. B. McN. Truscott and D. G. Bratherton (September 17, p. 857) may perhaps be due to the fact that some practitioners have in the past met with a few cases of cancer of the breast in which, in spite of delay, the growth was found still to be in an "early stage." There are a few such cases due to the slow growth of the individual tumours, but the complacency of such practitioners would be shattered if they looked at the figures in the Supplement on Cancer in the *Registrar-General's Statistical Review for the Year 1952*,[1] which show that a delay of six months reduces the number of early cases by over 30%.

It is to be hoped that the district nurses involved in such cases will not be deterred from their splendid efforts to obtain "early stage" diagnosis. Surely most practitioners must realize that every lump in the breast should be assumed to be malignant until disproved.—I am, etc.,

Malcolm Donaldson,
Hon. Secretary,
Cancer Information Association.

Reference

[1] *Registrar-General's Statistical Review of England and Wales for the Year 1952. Supplement on Cancer*, p. 13, Fig. B3, 1957. H.M.S.O., London.

Personal Record Cards

Sir,—Much has been written in recent years as to the necessity for information regarding the immunization state of any individual being readily available. Various suggestions have been put forward, one being that each individual should have an immunization record card. This policy has been tried out here and a subsequent assessment made as to its usefulness.

In this area the routine protection procedures are recommended to be given at the following ages:

Smallpox	4–5 months
Poliomyelitis 1st inj.	6–7 „
2nd inj.	7–8 „
Diphtheria, whooping-cough, and tetanus 1st inj.	9–10 „
2nd inj.	10–11 „
3rd inj.	11–12 „
Poliomyelitis booster	14–15 „
Triple booster	30–31 „

These may be given by a local-authority doctor or by the child's own general practitioner. If given by a local-authority doctor, a record card is made out at the time or the appropriate entry made on the card already issued to the parent. If the general practitioner gives the vaccination or inoculation, the health visitor at her next visit (and the health visitors are expected to see the children roughly at monthly intervals for the first six months, then at nine, 12, 18, 24, and 30 months) issues

and completes a card or enters the later details on the card already issued. Duplicate records are kept centrally for every child.

In an effort to check the usefulness of this, an inquiry was made relating specifically to the position of children at the age of 2½ years who as shown above were under regular supervision and who had commenced their injections at approximately 4–6 months. 1,596 children came into the survey. The findings were as follows:

Personal record cards not issued	253	16%
,, ,, ,, issued but not now available	221	14%
,, ,, ,, incomplete	269	17%
	743	47%

It would appear, therefore, that even in two years' time 30% of children who should have had record cards did not have them; and in a further 17% of cases the records were incomplete and therefore valueless and possibly even misleading. With the passage of time the position would obviously worsen steadily. These deficiencies can be attributed to little else than "personal" factors which are likely to be found universally. When one remembers that, in addition, the completed cards of those who have them may well not be available at the very time they are wanted, the only conclusion one can come to is that this is not a satisfactory method of dealing with the problem.—I am, etc.,

Health Department, Midlothian and Peeblesshire County Councils. JOHN RIDDELL.

Sewage in the Sea

SIR,—I am most grateful to Dr. J. C. Hill (September 24, p. 942) for pin-pointing so accurately the crux of this subject. He says quite simply, "I do not like bathing amongst faeces," and leaves it there. Dr. John D. Kershaw (September 24, p. 941) says almost the same thing when he confesses to "a particular prejudice against particles of infected faeces," but unfortunately he does not leave it there. I share fully Dr. Hill's dislike, and my prejudice goes further than Dr. Kershaw's in that it includes all particles, whether infected or not.

I think they will agree with me that as members of an honourable profession we must beware that our dislikes and prejudices do not influence the professional opinion we express either to patients or to public bodies. I cannot feel that this principle has been observed either at the Representative Meeting or in the correspondence which has followed. If, for example, someone grew pathogens from pound notes (and I seem to remember that someone did) and put forward the hypothesis that paper money was an important means of the spread of disease, he would have as much supporting evidence as there is for the hypothesis about the health dangers of bathing in sewage-polluted sea-water. He might say that contact with such infected articles must, in the words of Dr. F. J. G. Lishman (September 17, p. 865), remain dangerous until proved otherwise. If, then, the Medical Research Council published a report stating that careful investigation had failed to provide any evidence to support his hypothesis, I doubt whether the Annual Representative Meeting would go on record as being flabbergasted and alarmed by the report. Money, even if dirty, does not provoke the same disgust reaction as other people's faeces. Is Dr. Kershaw sure that his prejudice has not influenced his professional opinion? He should take warning from the example of Dr. H. Fidler (September 24, p. 941), whose emotional involvement in the subject is so deep that he permits himself the absurdity of describing my first letter as an "impassioned appeal for the right to bathe in sewage-polluted sea-water."

I was interested in Dr. P. H. Boshoff's contribution (September 24, p. 940). In my first letter (September 3, p. 734) I indicated that there were many good reasons (other than health) for changing the system of sewage disposal in coastal towns, and Dr. Boshoff now provides some evidence for yet another.

I shall not ask for space to reply in detail to the points raised by Dr. Lishman or Dr. Kershaw; if they are interested we can continue the discussion by private correspondence. I cannot, however, allow Dr. Kershaw to get away publicly with his attempt to transmute shellfish into red herring. The point investigated by the committee was the health risks of *bathing* in sewage-polluted water. The danger from shellfish taken from such waters has been long established and was not considered in the report or in subsequent correspondence. It was Dr. Kershaw alone who introduced it, and, important though it be, it was quite irrelevant here. If the Medical Research Council were to produce a report stating that the health danger from shellfish collected from sewage-polluted waters could be ignored, there would be a real occasion for the whole profession to join the Southampton Division in being flabbergasted.—I am, etc.,

Great Yarmouth. K. J. GRANT.

Deaths from Drowning

SIR,—I hasten to support Dr. F. W. Woodruff's plea (September 10, p. 798) for increased facilities for learning to swim. I was taught by my mother and her sisters while still a very small boy. I grew up to like the water and became efficient enough to swim for my hospital, the London. It is absurd for would-be instructors (as for music) to make out that all that is needed is "a little confidence." All should be methodically taught. Here is how I do it. Hold the beginner firmly, except for one leg. Let them learn one leg at a time. Further particulars, if desired.—I am, etc.,

121 Thorne Road, Doncaster. W. REGD. WILSON.

British Student Tuberculosis Foundation

SIR,—I should like to take this opportunity of bringing to your notice the appeal for money to run the British Student Tuberculosis Foundation. The Foundation was created 10 years ago so that sudents with the disease could continue their studies while having treatment. There are now two units—an English one at Pinewood Hospital in Berkshire, and a Scottish one at Tor-na-dee, near Aberdeen. Over 400 students have passed through our units and an impressive array of examination results has been produced. Any student attending an institute of higher education in a full-time capacity is eligible for the unit, and of these one in every thousand will require treatment for tuberculosis each year. This disease is no longer the scourge it once was, but it still is common, serious, and requiring prolonged treatment.

The Foundation needs £10,000 to pay for the cost of administration over the next few years—a small amount to ask in this day and age. Further information may be obtained and donations or covenants sent to the Secretary/Administrator, B.S.T.F., Pinewood Hospital, Wokingham, Berkshire.—I am, etc.,

E. J. R. ROSSITER, Chairman.

Treatment of Skeletal Tuberculosis

Sir,—We have read Mr. M. C. Wilkinson's letter under this heading (August 20, p. 598) with interest. Mr. Wilkinson doubts the possibility of obtaining excellent results in skeletal tuberculosis by prolonged antibiotic therapy alone, and says that necrotic and sequestrated areas cannot recover without surgical intervention.

This view seems to have been accepted not only in Britain but surprisingly also in Africa and India[1,2]; it is not borne out by our experience at Ibadan.[3]

We now have records of 70 patients suffering from cervical and thoracic disease who were treated without any surgery but with drugs given to them whilst wholly ambulant, plus plaster-of-Paris jackets when indicated by cervical disease or marked muscle spasm or weakness.

In 62 of these the perispinal abscesses absorbed completely. Of the 8 in whom the shadows remained 5 are not healed but are well, 2 are radiologically healed with abscess shadows remaining, and 1 is healed, the shadow having become smaller. Paraplegia did not develop under treatment. 34 of the patients have been followed up over 18 months.

A full account of the work of the Spinal Clinic at University College Hospital, Ibadan, is in preparation.—We are, etc.,

P. G. Konstam.
A. Blesovsky.

University College Hospital, Ibadan, Nigeria.

References

1 Mukopadhaya, B., *Ann. roy. Coll. Surg. Engl.*, 1956, **18**, 288.
2 Roaf, R., Kirkaldy-Willis, W. H., and Cathro, A. J. M., *Surgical Treatment of Bone and Joint Tuberculosis*, 1959. Livingstone, Edinburgh and London.
3 Konstam, P. G., and Konstam, S. T., *J. Bone Jt Surg.*, 1958, **40B**, 26.

London Medical Orchestra

Sir,—The London Medical Orchestra provides for members of the medical and allied professions an enjoyable and productive relaxation. Rehearsals take place every Thursday at 8 p.m. at the Rutherford School, Penfold Street, Marylebone, and new members would be welcomed by the Secretary, Dr. H. O. Engel, of 40 Warrington Crescent, W.9, especially those who perform on string or brass instruments.

Rehearsals lead to public appearances at scientific conversaziones and concerts in private houses. Once a year, too, a charitable concert with a guest soloist of renown is held. This year, with Ernest Cooper, a sum exceeding £500 was raised at the concert for the Imperial Cancer Research Fund.—I am, etc.,

A. Dickson Wright.

London W.1.

Medical Practice Centre

Sir,—May I draw the attention of your correspondent (October 8, p. 1087) to the centre which has already been set up at the College of General Practitioners, and add that advice is available to all members of the medical profession. A steadily increasing amount of information about premises, together with photographs and plans, is available, and also an exhibition of practice equipment.—I am, etc.,

J. C. T. Sanctuary,
Chairman, Practice Equipment and Premises Committee, College of General Practitioners.

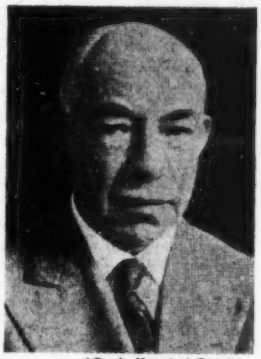
41 Cadogan Gardens, Sloane Square, London S.W.3.

Obituary

T. B. JOHNSTON, C.B.E., M.D.

Professor T. B. Johnston, emeritus professor of anatomy and formerly dean of the medical school and superintendent of Guy's Hospital, died at Nuffield House on October 8. He was 77 years of age. At Guy's he was one of the great personalities of his generation, and in the medical world outside the hospital he was famed as the editor of nine editions of *Gray's Anatomy*.

Thomas Baillie Johnston was born at Aldershot on July 23, 1883, the son of Major A. Johnston, R.A.S.C. Educated at George Watson's College and Edinburgh University, he graduated M.B., Ch.B. in 1906, proceeding M.D., with a gold medal for his thesis, in 1937. Soon after graduation he was appointed lecturer in anatomy at Edinburgh, and he remained there until 1914, when he moved to a similar post at University College, London. During the first world war he served as a captain in the R.A.M.C., and not long after his demobilization he left University College to become, in 1919, professor of anatomy at Guy's Hospital Medical School.



[*Guy's Hospital Gazette*

After nearly thirty years at Guy's he retired from his appointments there in 1948, though he remained actively at work on several projects until shortly before his death. He had been the British delegate to the International Congress of Anatomists in 1936, and fourteen years later he took on the secretaryship of the International Anatomical Nomenclature Committee. The first edition of *Gray's Anatomy* for which he was responsible was the 24th, published in 1928, and he was the senior editor of the centenary edition (the 32nd) published 30 years later. His *Synopsis of Regional Anatomy* first appeared in 1921, and the last edition was published in 1957.

Professor Johnston, who was a bachelor, was appointed C.B.E. in 1945.

A. H. D. writes: Medical students returning to University College, London, after the 1914–18 war found that a new and impressive figure had joined the anatomical teaching staff. T. B. Johnston, who had just left the Army to work as senior demonstrator, was clearly a man of outstanding qualities. He was in those days a benevolent martinet. Late arrival or inattention at his demonstrations would be dealt with by a few well-chosen and highly effective comments. No one who attempted the then popular pastime of ragging ever did so twice. He was worshipped, though held in awe, by the undergraduates—always quick to recognize efficiency and strength of character. His demonstrations of anatomy packed his theatre day after day. The subject became a living and applied science never to be forgotten by those who had the privilege of sitting at his feet.

All too soon for University College he left to occupy the chair of anatomy at Guy's Hospital. Such was his spell that more than one student followed him as disciples. At Guy's his teaching in the anatomy department enhanced his already high reputation, and drew postgraduates to him from many parts of the world. In spite of his heavy professional duties he accepted the onerous task of dean

of the medical school. As was to be expected, the school flourished under his administration. So greatly was he held in esteem by his preclinical and clinical colleagues that on the retirement of the hospital medical superintendent, Sir Herbert Eason, he was pressed to accept the post. His love was anatomy; and against personal inclination, and only after assuring himself that it was the unanimous wish of the staff did he agree, but he continued to control the anatomy department.

His ability was soon put to the test by the outbreak of war in 1939. He built up the E.M.S. service in the Guy's sector with complete success, and maintained it in a state of efficiency throughout the war. When hostilities ceased he returned to his dual role at the hospital until his retirement in July, 1948. Even then, as a governor of Guy's, he worked tirelessly for its good. His final illness was mercifully short-lived.

He was a man of great charm, kindness, and generosity. He was always willing to help and advise students on their problems. His exceptional memory of the names and even initials of those he had taught over the years was a gift which lasted almost up to the time of his death. His sense of humour was delightful, and as a host there was none better. Guy's was indeed fortunate in its choice, and mourns deeply its loss.

H. A. H. writes: I first met Thomas Baillie Johnston in the dissecting-room at University College, London, in October, 1916, when Great Britain was on the verge of starvation, the Western Front in danger of collapse, and U.C.H. crowded with wounded. Most of the staff of the Medical School and hospital were doing two jobs at the same time, one of which involved the wearing of the uniform of the R.A.M.C. The newly built Galton Laboratory of Eugenics in University College was transformed into a temporary hospital before the plaster on the walls had dried out.

"T.B." had come from Edinburgh in 1914 as lecturer and senior demonstrator to serve under Professor George Dancer Thane, who appeared to be able to guide and even "boss" the College, the Medical School, the hospital, the Home Office (vivisection licences), and various committees concerned with the call-up of doctors and the return of medical students from the Services to complete their medical studies. Thane wielded great influence without wasting time on endless committees or chasing politicians.

Thane lectured three mornings a week, ran various full-dress demonstrations on dissected bodies, and held two written examinations each term for both seniors and juniors. "T.B.," with the help of members of the hospital staff ranging from consultants and registrars to mere housemen, ran a series of demonstrations in the small theatre adjoining the dissecting-room and did the round of the cadavers undergoing dissection with method and purpose. He maintained the high standard of accuracy and precision which Thane demanded. He was an excellent teacher in the Scots manner, but his sense of humour saved the student from the boredom that is so often associated with the Edinburgh School.

Thane retired in 1919 and was followed by that brilliant and stimulating genius, Grafton Elliot Smith, who cast so much light on neurology, anthropology, Egyptology, and human biology. At the same time "T.B." was elected to the new chair of anatomy in Guy's Hospital Medical School. In the nineteenth century Guy's Hospital had produced Hodgkin, Bright, John Hilton, Charles Hilton Fagge, and William Gull, a run of giants which has only been surpassed in Dublin.

"T.B." soon became a power in Guy's. He became dean and eventually governor of the hospital. He accepted the arduous task of editing *Gray's Anatomy*, which was distributed far and wide over the Colonies and the East in general. He became interested in the vexed question of anatomical terminology, a problem which was laboured by the publishers rather than the anatomists. I told him that I preferred the Psalms in the Authorized Version rather than in the Scots metrical version. One is tempted to regret that the Medical School at Guy's should have profited less from his great anatomical knowledge than from his ability as organizer and administrator. Two wars changed many of men's desires and hopes.

Those of us who have passed the allotted span of three-score years and ten will always cherish the memory of Thomas Baillie Johnston as teacher, friend, and considerate uncle to those in difficulty. I often persuaded him to accept in Guy's a young student who had been unable to stand up to the sport and social round of Cambridge. This was a side of his character which I loved more than I can tell.

Thomas Baillie Johnston extended the bailiwick of Guy's Hospital. The extension of the hospital, the nurses' home, the erection of new laboratories, combined with the spirit of Thomas Guy, may yet provide the answer to so many of the unsolved conundrums propounded by Hodgkin, Bright, Hilton, Fagge, and Gull. If this rebirth takes place then a great deal of the credit will be due to "T.B.'s" love of the place he adopted, an outlier of St. Thomas's, as the Middlesex was an outlier of U.C.H.

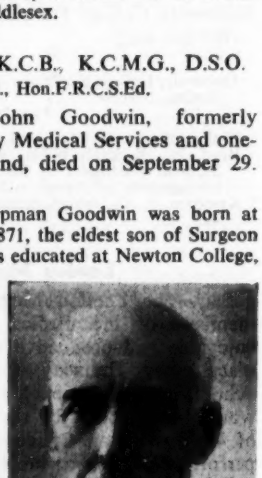
For the consolation or edification of the "angry young people" may I add that "T.B.'s" wage as lecturer and senior demonstrator at U.C.L. was £300 per annum. At the same time Tim Yates at the Middlesex Hospital Medical School for a similar task, with no professorship as yet established, was in receipt of £250 per annum. This meagre scale of salaries never broke the spirit of the Scot in U.C.L. or of the Irishman in the Middlesex.

Sir JOHN GOODWIN, K.C.B., K.C.M.G., D.S.O.

Hon.D.Sc., F.R.C.S., Hon.F.R.C.S.Ed.

Lieutenant-General Sir John Goodwin, formerly director-general of the Army Medical Services and one-time Governor of Queensland, died on September 29. He was 89 years of age.

Thomas Herbert John Chapman Goodwin was born at Kandy, Ceylon, on May 24, 1871, the eldest son of Surgeon Major John Goodwin, and was educated at Newton College, Devon, and at St. Mary's Hospital, London, qualifying M.R.C.S., L.R.C.P. in 1892. Commissioned in the Army Medical Service in 1893, he came third in his group at Netley. As staff surgeon in the Mohmand field force on the North-west Frontier of India, he was mentioned in dispatches and awarded the D.S.O. for his services in the battle of Shabkadar in 1895. He again distinguished himself in the first world war, in which he served with the British Expeditionary Force at Mons, on the Marne, at Ypres, and elsewhere. He was three times mentioned in dispatches, and was appointed C.M.G. in 1915, by which time he had attained the rank of lieutenant-colonel. For a period he was in command of No. 14 General Hospital at Wimereux.



[Bassano

In May, 1917, Goodwin was appointed to accompany Mr. Balfour's mission to the United States of America as representative of the Army Medical Department—he was assistant director of medical services at that time—and did much to facilitate the cordial co-operation between the U.S.A. and the British Army medical service. Though quiet and unobtrusive, he was always very well informed, and Lord Northcliffe, among other prominent men of the day, thought highly of his ability. Early in 1918, Colonel Goodwin—as he then was—was appointed deputy director-general of the Army Medical Services, and in the following

March succeeded the late Sir Alfred Keogh as director-general. Later in the same month he was appointed C.B. for valuable services rendered in connexion with the war, being promoted K.C.B. in 1919. He held the appointment of director-general until 1923, when he retired. During the latter part of his Army career he was an Honorary Surgeon to the King. Goodwin was colonel commandant—the first—of the Army Dental Corps from 1927 to 1932, and of the R.A.M.C. from 1932 to 1938. He was promoted K.C.M.G. in 1932, the year in which he relinquished the office of Governor-General of Queensland, to which he had been appointed in 1927. To this work he brought the same tact and enthusiasm that had characterized his Service career, and when his term of office ended he left behind many friends in Queensland, and widespread regret at his departure. Queensland had already had a member of the medical profession as Governor in the person of Sir William MacGregor, who held the office from 1909 to 1914.

Goodwin's ability and his services were recognized by honours conferred on him both at home and abroad. He was a Knight of Grace of the Venerable Order of St. John of Jerusalem. In 1919 he was admitted a Fellow of the Royal College of Surgeons of England, an honorary Fellow of the Royal College of Surgeons of Edinburgh, and an honorary Freeman of the Society of Apothecaries of London. He also received the honorary Fellowship of the Royal Australasian College of Surgeons, was elected a Fellow of the American College of Surgeons, and awarded the honorary degree of D.Sc. by Oxford University and the M.A. of Michigan University. He was appointed a Commander in the French Legion of Honour, in the Belgian Order of Leopold, and in the Italian Order of the Crown, and was awarded the Belgian Croix de Guerre and the American Distinguished Service Medal. He was the author of *Field Service Notes for the R.A.M.C., Notes for Medical Officers on Field Service in India, Notes for Army Medical Officers, Prevention of Disease on Active Service,* and *Making a Shoot.*

In 1897 General Goodwin married Miss Lilian I. Ronaldson, and she survives him. His younger brother, Colonel W. R. P. Goodwin, formerly assistant director-general of the Army Medical Services, died in 1958.

MAX LOEWENTHAL, M.D., M.R.C.P.

Dr. Max Loewenthal, who had once worked with Sir Victor Horsley and Sir Charles Sherrington, and later was in practice in Liverpool, died in Johannesburg on October 8 at the age of 92.

Max Solly Loewenthal was born in Germany on October 10, 1867. He studied medicine at the University of Würzburg and graduated M.D. in 1892. He came to London two years later, qualifying L.S.A. and taking the M.R.C.P., both in 1894. At the time of his death he had been a member of the Royal College of Physicians of London longer than any other member now alive. For the first few years of his life in England Loewenthal worked as a neurophysiologist with Sir Victor Horsley at University College, and his research there was of exceptional importance. Later he moved to Liverpool, where he was in general practice from 1897 to 1935. In 1924 his paper in this journal on the use of amidopyrine in measles was widely read. He came to the conclusion that this drug was specific in measles, and it was in fact used by many for the treatment of measles until the association of amidopyrine with agranulocytosis was reported.

Dr. Loewenthal moved to South Africa on the death of his wife and lived there in retirement. Apart from his contributions to medicine he was also interested in physics and mathematics, on which he was the author of some papers. In 1930 his book *Life and Soul,* containing his theory of the origin and meaning of life, was published.

Dr. Loewenthal died two days before his 93rd birthday, and he is survived by a son, Dr. L. J. A. Loewenthal, who is a dermatologist in Johannesburg, and by a daughter.

Sir Arthur MacNalty writes: As is well known, Sir Victor Horsley, besides collaborating with E. A. Schäfer, C. E. Beevor, and R. H. Clarke, from his early days welcomed and encouraged young men with an aptitude for research. He invited them to his private laboratory in University College and inspired and directed their researches on the central nervous system. One of these workers was Max Loewenthal, who has just died, a nonagenarian, in South Africa. In the course of assisting Horsley in an experiment, he observed that in the experimental animal when both cerebral hemispheres were removed active extension tonus of the limbs was obtained (acerebral tonus). It was further noticed that faradic excitation of the upper surface of the cerebellum caused immediate relaxation of such tonus so long as the current was applied, and that on the current being shut off the tonus was re-established.

The observation indicated a distinct relation between the cerebellum and the bulbo-spinal system of the lower centres, and Loewenthal and Horsley entered on an experimental research on the subject. Their experiments proved that acerebral tonus was a constant effect. For instance, the muscles of the right arm could be influenced by excitation of both halves of the cerebellum, but the effect is much greater from excitation of the right half—that is, on the same side. They also confirmed Sherrington's discovery that excitation of the right afferent tract on the same side causes relaxation of triceps and contraction of biceps, while excitation of the left afferent tract causes relaxation of biceps and contraction of triceps, an interesting correspondence with the alterations they observed in the two halves of the cerebellum, which obviously related to the movement of progression.

These important discoveries were recorded in a paper read before the Royal Society entitled "On the Relations Between the Cerebellar and Other Centres (namely, Cerebral and Spinal), with Especial Reference to the Action of Antagonistic Muscles," by Max Loewenthal and Victor Horsley (*Proc. roy. Soc.*, 1897, **61**, 20–25). It was published as a preliminary communication and the authors intended to extend their researches. Sherrington was working on the same subject, and the studies he had already made on decerebrate rigidity rendered further work unnecessary. In any case Loewenthal could not continue to work with Horsley, for in the same year, 1897, he had decided to take up general practice in Liverpool.

Sherrington, who was professor of physiology at Liverpool University, later encouraged Loewenthal to enter on a further research entitled "Experiments on the Conductivity of the Spinal Cord Rendered Anaemic by Compression of the Aorta" (*Brain*, 1902, **25**, 274–285). The experimental work on cats was done in the physiological department of the Thompson-Yates laboratories, Liverpool. Loewenthal's conclusions were as follows: (1) The first effect of arrest of circulation on the functions of the spinal cord is an increase in readiness and strength of interneural transmission of nerve energy lasting about 30 seconds. (2) After from 1 to 2 minutes stimuli approaching the grey matter through peripheral nerves or fibres of the white substance are not transmitted to the lower motor neuron. (3) It is probable that every single neuron as a functional unit retains its vitality for a period exceeding 15 minutes, but the mechanism which links the separate neurons together is quickly destroyed by death. (4) The existence of spinal fits cannot be disputed. The spinal fits were chiefly tonic. They originated in the grey matter of the spinal cord and occurred after conduction from the cerebral cortex was abolished.

Thereafter the responsibilities of general practice intervened, and Loewenthal found no time for further researches in neurophysiology. With Horsley he had written one of the most fundamental papers on the subject. It led Horsley to pursue further research work on the cerebellum. As Sir Geoffrey Jefferson observes (*Brit. med. J.*, 1957, **1**, 906): "Moruzzi (1950) has said that the discovery by Horsley and Loewenthal as well as by

Sherrington, that stimulation of the anterior median cerebellar cortex inhibited decerebrate rigidity, equalled in its revelation of cerebellar function the discovery of the excitability of the motor cortex."

ELIZABETH J. MOFFETT, M.D., B.Sc.

Dr. Elizabeth J. Moffett died in Birmingham on September 23, aged 93. One of the oldest women doctors in Britain, she worked for most of her professional life in the school medical service, first in Stafford and then in Birmingham.

Dr. D. Beaumont writes: Elizabeth Jane Moffett, who was born on November 10, 1866, was the second eldest of the large family of a Congregational minister who came from Northern Ireland. She went to the pioneer school of Milton Mount, Gravesend, and in 1885 won a scholarship to the recently opened University College of Bangor, where, as she said, she "was converted to Darwinism." In 1889 she won an entrance scholarship to the London School of Medicine for Women, where she had Schäfer, Halliburton, and Hector Mackenzie as lecturers. Dr. Moffett noted, "We warmed our lotions in pans on an open fire. No nurses in attendance. Nurses were somewhat antagonistic." In an address given on her eightieth birthday, she recalled her first "social" case: "A french-polisher, out of work, with a fractured bone in the palm. No union occurred, so I got dinner tickets from Matron and, hey presto! the bone healed." (Some years later she was asked if she had taken a social science diploma. "No," she said, "I have been practising it for 50 years.")

In 1893 she spent a happy year at Great Ormond Street Hospital, and graduated M.B. (London) in the following year. In 1895 she took her first post at Mullingar Asylum, Ireland, but she returned to England in 1897, was house-surgeon at the National Hospital for Women, working under Mrs. Scharlieb, Dr. Jane Walker, and Miss Aldrich-Blake. In 1898, after proceeding M.D., she started practice in Kilburn. "An uphill trek" was how she described it.

In 1908 she entered the school medical service in Stafford and spent five happy years under Sir Graham Balfour, Dr. George Reid, and Dr. Priestley. Margery Fry was on her committee. Dr. Moffett "made reports on school buildings, defective drainage in a village, and on overcrowding. This sometimes made one unpopular with the managers and landlords. Sometimes one had to stand up to the committee." During the next few years she took an active part in the women's suffrage agitation. In 1913 she transferred to Birmingham, where, as she said, "many facilities were available." During the first world war she was attached to the R.A.M.C. in Malta, looking after men evacuated from Salonika. On her return to Birmingham she undertook spare-time work with the Birmingham Invalid Children's Association, helping particularly with rheumatic and delicate children.

She described the school medical service as a specialty, giving it her own flavouring of social work. "I had been told," she said, "not to trouble myself about the social condition of the children, but I carried on as before. The school service has always been the Cinderella." She retired in 1931, but carried on with ophthalmic work for some years and with social work, mainly among children, as long as she could. A keen and active member of the Medical Women's Federation, she celebrated her eightieth birthday by describing much of her life in a speech at a meeting of the Birmingham and District Medical Women's Association.

At 92 she was persuaded to give up her home because of physical infirmity, and she spent her last two years at Bryony House. Although physically infirm, she retained her lively mental facilities until the end and was reading Dr. Schweitzer's book four days before she succumbed to pneumonia. And so we have lost another pioneer, a good fighter, unafraid, with much compassion for the families she met in her work.

J. M. TAIT, O.B.E., M.D.

Dr. J. M. Tait, for thirty years one of the leading practitioners in Sutton, Surrey, died on September 3 after a prolonged illness. He was 54 years of age.

James Melrose Tait studied medicine at Newcastle upon Tyne, graduating M.B., B.S., with honours, at the University of Durham in 1928, being gold medallist of his year. He proceeded M.D. two years later. After holding several appointments at the Royal Victoria Infirmary in Newcastle he entered practice in the Sutton area and remained there all his professional life apart from his service in the R.A.M.C. during the second world war, at the outbreak of which, being a Territorial, he was called up to serve with a field ambulance. He later served with the 44th Division and attained the rank of Lieutenant-colonel. At the end of the war he was appointed O.B.E. for his services.

Tait was for many years on the staff of the Carshalton War Memorial Hospital, and did much good work as a general-practitioner surgeon. He latterly became chairman of the medical staff. He joined the staff of Sutton and Cheam Hospital as an obstetrician before the advent of the National Health Service, and retained this appointment until ill health necessitated his retirement last April.

J. K. H. S. writes: The tragic death of Jim Tait at the height of his powers came as a great shock to his friends and colleagues in the Sutton and Carshalton area. He could have had a career as a surgeon in the North, had he so desired, for he had been a brilliant student, but he elected to enter general practice in Carshalton after completing his house jobs. He did fine work at the Carshalton War Memorial Hospital as a general-practitioner surgeon for many years, but later transferred his gifts and energy to obstetrics.

Tait was the embodiment of all that is finest in the general practitioner. An expert clinician, he gave his whole time and experience to his large practice. Those who did not know him intimately found him at times a little distant in his manner, but this was due entirely to a certain shyness in his make-up. He was kindness itself, and ever ready to give any assistance when asked.

To his friends he could be a delightful companion with a great sense of fun. Though he had little time for leisure he was a keen rugby supporter and an enthusiastic, if not very successful, golfer. He was born of true Northumbrian stock, and part of his heart remained in the Border country of the Cheviot Hills. A day's shooting gave him great delight all his life.

Tait was not afraid to admit to being a practising Christian, and those who knew him intimately were aware of the strength which his faith gave him to face with courage and fortitude what he must have known would be the fatal end to his illness. There are many colleagues and countless patients who have reason to mourn the passing of Jim Tait. He was indeed a fine doctor and a Christian gentleman.

A. SIMPSON WELLS, M.D., F.R.C.S.Ed.

Dr. A. Simpson Wells, honorary consulting obstetrician to the Peninsula Maternity Hospital, Capetown, South Africa, died at his home at Rondebosch on September 8, five days after his 85th birthday.

Alexander Simpson Wells was born at Glasgow on September 3, 1875, the son of the Rev. J. Wells, and was educated at Glasgow Academy and High School. He then

entered Glasgow University as a medical student, graduating M.B., Ch.B., with commendation, in 1899. He was elected a Fellow of the Royal College of Surgeons of Edinburgh in 1903, and proceeded to the M.D. in 1910. After graduation he held the appointment of house-surgeon at the Glasgow Royal Maternity Hospital, having held a similar post at the Western and Royal Infirmaries in the city. In 1900 he served in the South African Field Force as a civil surgeon, attaining the rank of major, and for a time was plague medical officer under the Government of Cape Colony. He held the same rank in the South African Medical Corps during the first world war, serving in the campaign in German South-West Africa. Dr. Simpson Wells settled in practice in Capetown in 1903, and after the first world war became honorary physician to the Peninsula Maternity Hospital and lecturer in clinical obstetrics in the University of Capetown. A member of the British Medical Association for nearly 60 years, he was president of the Cape of Good Hope–Western Province Branch in 1920. He served on the Branch Council for a number of years, and in 1924–5 was representative of the Branch on the South African Committee.

Sir GORDON GORDON-TAYLOR, K.B.E., C.B. M.D., F.R.C.S.

The obituary of Sir Gordon Gordon-Taylor was published in the *Journal* of September 10 (p. 807).

Sir William Johnston writes from Melbourne, Australia: The news of the tragic death of Sir Gordon Gordon-Taylor has brought sadness to innumerable friends in Australia—friends who revered him not only for his surgical eminence but also for his lovable human qualities. Kindliness, helpfulness, and warmth of feeling he gave out in full measure throughout the many years of his long life to the benefit and delight of successive generations of Australians.

His love of this country and its people was a very real one. His interest was first aroused when he met Australians while teaching anatomy for the primary Fellowship of the Royal College of Surgeons at the Middlesex Hospital in the first decade of this century, and he was wont to recall with pride those, including Balcombe Quick, Fay Maclure, Gordon Shaw, and others, afterwards to achieve honoured positions as surgeons in this country, whom he had first come to know in this way. This feeling was strengthened by contacts in forward surgical units in France during the first world war, when his experience and help were constantly given to our medical officers. From then on his interest in the members of the profession in Australia and New Zealand continued to grow, and was renewed in the course of several visits to these countries. He conferred valuable benefits of a varied nature on our profession in Australia on these occasions. He acted as examiner for the primary F.R.C.S. examination in 1934; he delivered the George Adlington Syme Oration to the Royal Australasian College of Surgeons in 1947; he made a memorable contribution on "Surgical Aspects of Management of the Complications of Peptic Ulcer" at the B.M.A. Congress in Melbourne in 1952. At these times it was one of his great joys to live in one or other of the teaching hospitals, where he was able to share the life of the young resident medical officers and senior students. For them it was an unforgettable experience and they loved it, meeting this remarkable personality, old in experience yet young in outlook, indefatigable in work yet able to joke and laugh with them, full of learning yet carrying it so lightly.

It was to the younger men in particular that he was drawn—those treading the difficult path of early post-graduate study, whether with the Fellowship of the Royal College of Surgeons or with further surgical experience in view. Nothing was too much trouble for him in the way of advice or inquiry if it were to benefit them, and his regular attendance at the Royal College of Surgeons for this purpose was an inestimable boon to these young aspirants.

It was a fitting indication of their esteem that a number of Fellows of the Royal Australasian College of Surgeons subscribed to a fund for the painting of his portrait. This was an expression of feeling on their part that gave him infinite pleasure. By a grim stroke of fortune his end came shortly after the presentation of this portrait to the College at the Annual Meeting in Adelaide.

But, although he had a special affection for the younger men, he included all ages and ranks within the wide circle of his friendship. His list of Christmas greetings to this country was immense, and a Christmas card from "G-T" was indeed something to be prized—each chosen with such care and inscribed with some charming individual message. And who of the many he has entertained in London with such cordial hospitality can look back without delight to the occasion of lunch at the Ritz with "G-T"—the perfect host so immaculate and charming, the window table overlooking Green Park, the delicious meal so carefully ordered beforehand, the staff so anxious to please him and his guests.

It was in keeping with his chivalrous character that among the few words spoken by him after his fatal accident were those exonerating the driver of the car that struck him down.

We in this country have lost a great friend. His memory will live on for many a year as surgeon, as benefactor, as scholar, and as one who helped so many over the rough places and made life sweeter for us all. Let us remember him in the words he applied to George Adlington Syme, written of Montrose by John Buchan: "His qualities in the retrospect seem to be drawn to a fine edge of burning light, but as we wonder and revere there comes a voice from behind the flame, and awe is turned to wistfulness, for it is a voice of comradeship and joy and youth."

Mr. R. W. Raven writes: May I be permitted to add a brief note to the full obituary notices of this great surgeon, for I hold in cherished memory my conversation with him on the day preceding his fatal accident? Sir Gordon was full of the joy of living, and his active mind was ranging over many subjects and contemplating a visit to Pakistan with obvious delight. He told me with enthusiasm of his preparations for an important lecture he had been invited to deliver, and with his inimitable smile informed me that the title was "The Drums of War and the March of Surgery." How eminently fitted he was to present such a subject, but, alas, we shall never be privileged to hear him speak again using choice language with such eloquence. Many of us recall with thankfulness the many acts of kindness to younger surgeons and the appropriate word of encouragement which meant so much. Sir Gordon lives on in the hearts of surgeons all over the world; we can never forget him, for he created a fellowship that is abiding and untouchable by death. And as we say good night to him it is with the lively hope that we shall meet him again when morning breaks.

Medico-Legal

CONDUCT DISGRACEFUL IN A PROFESSIONAL RESPECT

[From our Legal Correspondent]

An appeal by a veterinary surgeon to the High Court against an order of the Disciplinary Committee of the Council of the Royal College of Veterinary Surgeons was heard by the Divisional Court of the Queen's Bench Division on October 11 (*The Times*, October 12). On November 12, 1959, the Disciplinary Committee had found that the veterinary surgeon had been convicted of criminal offences and also had been guilty of conduct disgraceful in a professional respect. On those findings the Committee ordered his name to be removed from the *Register*.

Both the convictions in question were admitted. One concerned the offence of driving while under the influence of a drug, and the other dangerous driving. Before these offences the veterinary surgeon had submitted to treatment for alcoholism, and in the course of treatment was given paraldehyde, to which he became addicted. On the day of the offences he was under the influence of the drug, and did not know what he was doing. It was on the basis of these convictions that the Committee held him to be guilty of conduct disgraceful in a professional respect, but at the hearing of the appeal it was conceded on the Committee's behalf that this particular finding was wrong. On that concession, and in view of the nature of the offences, the Court allowed the appeal against erasure and substituted an order of suspension for two years.

Power of Suspension

Like medical practitioners, a veterinary surgeon may be disciplined either as a result of conviction of a criminal offence or where he is proved to have been guilty of professional misconduct: the Veterinary Surgeons Act, 1881, refers to "conduct disgraceful to him in a professional respect," while the Medical Act, 1956, refers to "infamous conduct in any professional respect." The two professions differ, however, in that the Disciplinary Committee of the General Medical Council can impose only one sentence—namely, erasure from the *Register*; while a veterinary surgeon may be sentenced by his Disciplinary Committee either to erasure, or to have the registration of his name made ineffective for a stated period. The General Medical Council resorts to the procedure of suspending sentence in certain cases, to supplement the lack of the power of suspension.

This decision does not go beyond saying that the facts of these particular offences did not justify a finding of conduct disgraceful in a professional respect. It might be that a conviction on other facts would in itself justify a finding of disgraceful or infamous conduct. However, it is never necessary to make such a finding on proof of a conviction, since proof of the conviction alone gives the Disciplinary Committee jurisdiction to impose sentence. The additional finding is unnecessary, and may provide grounds for appeal.

LADY HOARE AND THE LONDON CLINIC

[From our Legal Correspondent]

Lady Hoare, of Harley House, Marylebone Road, St. Marylebone, has recently taken out further proceedings against the London Clinic in connexion with the illness of her husband. Following her unsuccessful proceedings in the House of Lords (*Journal*, April 9, p. 1142), Lady Hoare took out proceedings in Bloomsbury County Court. However, the Registrar made an order staying further action on the grounds that the issues raised gave no cause of action, and refused leave to amend the claim by adding alternative claims for breach of warranty and for the return of certain of the fees paid by her. From this order, Lady Hoare appealed to the County Court Judge, Sir Alan Pugh, who rejected the appeal (*The Times*, October 6). The Judge held that Lady Hoare's present claims raised no fresh issues which had not already been adjudicated upon, and she therefore ought not to be allowed to continue. Although Lady Hoare had suggested that there had been surprise, fraud, and suppression of evidence, the judge held that none of these suggestions had been substantiated.

Universities and Colleges

UNIVERSITY OF LONDON

The title of Reader in Haematology in the University of London has been conferred on Dr. Sidney Shaw, and that of Reader in Bacteriology in the University of London on Dr. H. I. Winner, in respect of their posts at Charing Cross Hospital Medical School.

Vital Statistics

Causes of Death in 1959

Fewer deaths from whooping-cough occurred in England and Wales during 1959 than ever before: of the total of 25 deaths, 16 were of infants under 1 year of age and 9 of young children aged 1 to 4 years. The total of 66 deaths attributed to poliomyelitis is the lowest in any year since records began in 1911: it compares with 129 deaths in 1958 and 643 in 1949. Deaths from coronary disease and angina totalled 84,922 (52,193 men and 32,729 women): the greatest number of male deaths from this cause (19,219) was in the age-group 45 to 64, and of female deaths (15,794) in the 75 and over age-group. There were 21,063 (18,181 male and 2,882 female) deaths from cancer of the lung, an increase of 1,243 over the 1958 figure. Road accidents caused 6,026 deaths (4,414 men and 1,612 women): among men the greatest number of deaths (1,240) occurred in the age-group 15 to 24, but among women the greatest number (388) was in the age-group 45 to 64. All other types of accident caused 11,278 deaths, equally divided between the sexes.

Calculated according to the mortality figures of 1959, the loss of years of working life at ages 15 to 64 for every 10,000 men was: 114 for cancer, 113 for heart disease, 95 for accidents, and 79 for bronchitis and pneumonia. The corresponding figures for women were 96, 47, 26, and 45 respectively.—*The Registrar-General's Quarterly Return for England and Wales*, 2nd quarter, 1960.

Infectious Diseases

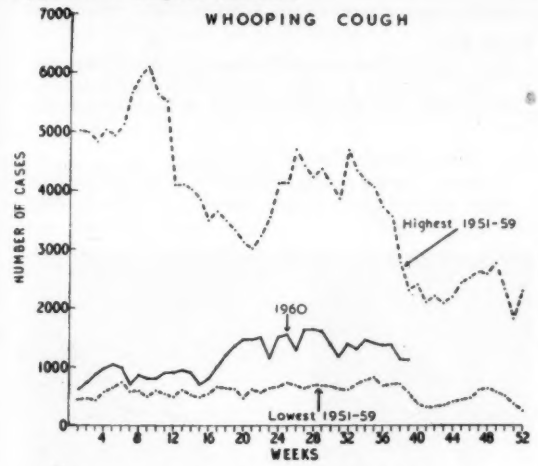
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

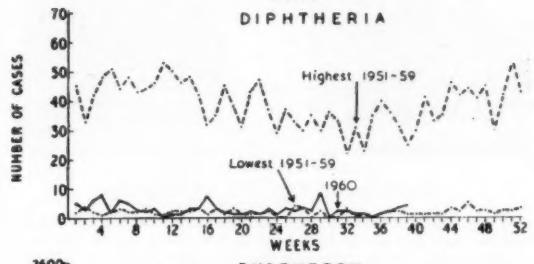
	Week Ending Oct. 1	Week Ending Oct. 8
Measles		
Lancashire	677	934
Burnley C.B.	97	86
Liverpool C.B.	91	82
Oldham C.B.	34	117
Dysentery		
Lancashire	67	87
Liverpool C.B.	21	27
London	64	112
Finsbury	22	25
Islington	8	15
Wandsworth	4	38
Middlesex	23	45
Edmonton M.B.	10	23
Staffordshire	21	20
Newcastle-under-Lyme	19	16
Yorkshire North Riding	14	20
Middlesbrough C.B.	10	12
Yorkshire West Riding	69	46
Leeds C.B.	28	15
York C.B.	5	10
Glasgow	142	80
Food Poisoning		
Lancashire	68	55
Liverpool C.B.	21	23
Kirkby U.D.	21	10
Surrey	26	25
Carshalton U.D.	21	16
Diphtheria		
Devon	2	2
Plymouth C.B.	2	2

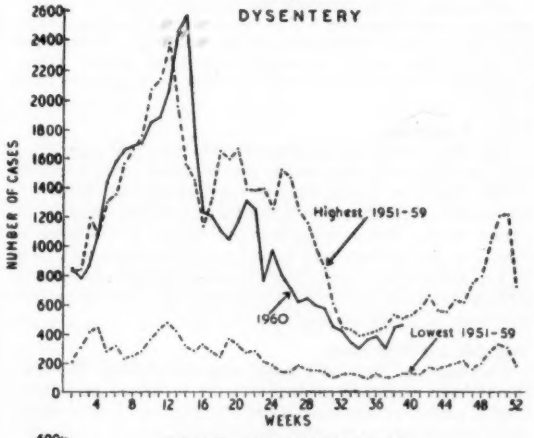
Graphs of Infectious Diseases

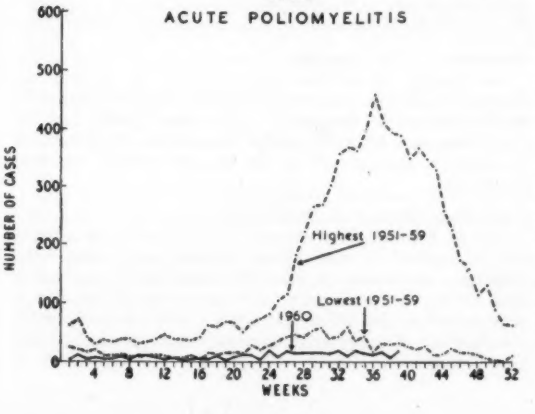
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifi-

cations in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 1** (No. 39) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	4	0	0	0	3	2	2	0	0	
Dysentery	477	64	185	6		503	55	305	8	3
Encephalitis, acute	1	0		0		5	0		0	
Enteric fever:										
Typhoid	5	3	2	1		5	1	0	1	1
Paratyphoid	6	0	1	1		7	0	0	0	18 (B)
Food-poisoning	287	29	20	9		269	32	30	1	
Infective enteritis or diarrhoea under 2 years				18	33				20	39
Measles*	1,891	86	59	4	7	794	26	12	18	31
Meningococcal infection	19	3	7	0	1	11	0	21	1	
Ophthalmia neonatorum	24	1	1	0		19	1	7	0	
Pneumonia†	175	9	114	4	1	174	11	131	4	3
Poliomyelitis, acute:										
Paralytic	12	6	0	} 0	6	{ 23	1	0	} 1	
Non-paralytic	6	1	0			{ 11	0	0		
Puerperal fever§	153	31	9	0		195	35	21	2	
Scarlet fever	305	15	45		22	605	55	109	14	28
Tuberculosis:										
Respiratory	386	50	50	15		365	41	56	20	
Non-respiratory	50	4	11	3		51	6	5	1	
Whooping-cough	1,110	117	101	9	20	639	37	92	11	16

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	1	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	1	1	0	0	9	0	1	0	1
Influenza	7	0	1	1	0	5	0	0	0	0
Measles		0	0	0	0		0	0	0	
Meningococcal infection		0	0				0	0		
Pneumonia	431	46	16	19	5	320	25	23	10	7
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 61	{ 3	3	2	3	} 60	{ 5	2	2	1
Non-respiratory		{ 0	0	0	0		{ 0	2	0	0
Whooping-cough	0	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	280	27	21	7	11	286	29	17	8	9
Deaths (excluding stillbirths)	9,026	749	605	133	124	8,255	617	502	111	143
LIVE BIRTHS	15,478	1327	1035	290	300	14,542	1197	1075	275	428
STILLBIRTHS	269	18	18			272	23	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

"The Hospital Gazetteer 1960"

The first edition of *The Hospital Gazetteer*, a guide to hospitals in the United Kingdom prepared by the B.M.A., has now been published (see *Journal*, September 10, p. 793), and may be ordered from the Publishing Manager, British Medical Association, B.M.A. House, Tavistock Square, London W.C.1 (price 5s. net, by post 6s.).

The gazetteer has been especially designed to help the doctor seeking a junior hospital appointment to choose the one most suited to his needs. (Mental hospitals are not included.) Information is given about the number of beds, the establishment of resident medical staff, the type of work and nature of special departments, qualifications and opportunities for preparation for postgraduate diplomas, the kind of accommodation provided, facilities for recreation, and other relevant facts. There is a special section on courses of instruction for higher degrees and diplomas provided by universities and other institutions. As the *Journal* annotation said: "With this guide in his hand the would-be resident will be able to survey the field from an armchair."

Harveian Oration

The Harveian Oration of the Royal College of Physicians of London was delivered at the College on October 18 by Sir Francis Fraser. His oration, on "The Challenge to the Medical Profession," will appear in full in the *Journal* in due course.

Centenary, King Edward Medical College, Lahore

The centenary celebrations of the King Edward Medical College, Lahore, Pakistan, will be inaugurated by the President of Pakistan on November 16. The three-day programme includes a series of lectures and a clinico-pathological conference. The Centenary Oration will be delivered by Lieutenant-Colonel S. M. K. Mallick, dean of the faculty of medicine, University of the Punjab. The University will also hold a Special Convocation in honour of the occasion. Many distinguished medical visitors will be present from the United Kingdom, other Commonwealth countries, and the United States of America. Members of the medical profession who have been associated with the College and would like more information about the celebrations should write to Mr. Ismet Anwar, Secretary, Centenary Committee, King Edward Medical College, Lahore, Pakistan, or to Lieutenant-Colonel Fahim A. Khan, Medical Adviser to the High Commissioner for Pakistan in the United Kingdom, 35 Lowndes Square, London S.W.1.

Wellcome Trust's New Member

Professor J. McMichael, F.R.S., has been appointed a Trustee of the Wellcome Trust in place of Sir Henry Dale, O.M., F.R.S., who retired from the Trusteeship in July and was succeeded as chairman by Lord Piercy. Professor McMichael's appointment became effective on October 10.

General Practitioner Research Group

This group, which was formed to undertake clinical trials in general practice, has recently been awarded a research grant by the National Institutes of Health, U.S. Public Health Service. The grant, of $5,000 a year for two years, is to be used for the "investigation of the value of various tranquillizing and other psychotherapeutic drugs in general practice." General practitioners interested in taking part in this investigation are asked to communicate with the director of the group, Dr. David Wheatley, at 270 Staines Road, Twickenham.

Old Feet

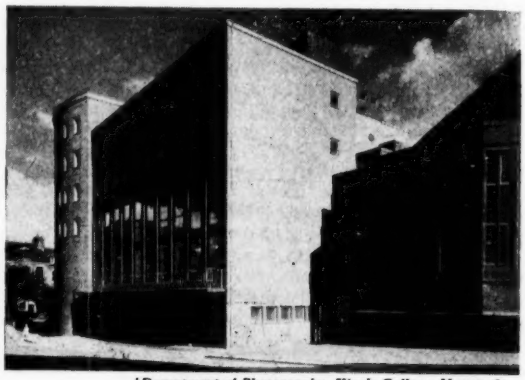
The National Corporation for the Care of Old People has issued a report, *Chiropody for the Elderly*, on the results of a three-year study of 120 voluntary schemes. The Corporation believes that a national chiropody service for old people is a necessity, while a survey of 120 individual cases shows chiropody to be "of great benefit as regards physical comfort, the maintenance of mobility and improvement in morale of the patients," and "a valuable factor in maintaining the physical and mental health of the elderly." (N.C.C.O.P., Nuffield Lodge, Regent's Park, London N.W.1, price 2s. net.)

Young Feet

Research into foot defects in children is to be carried out by Guy's Hospital, London, and Salford Royal Hospital, with the help of a grant from the Sir William Coxen Trust Fund.

New Library, King's College, Newcastle

A library, costing nearly £400,000 to build and including a large medical section, was opened recently at King's College, Newcastle.



[*Department of Photography, King's College, Newcastle*

The new library, King's College, Newcastle.

It seats 750 students and staff and houses almost 500,000 books. Among these are all the books the college possessed 90 years ago—few enough to fit into one glazed case. There is a main six-story central building, with an east wing of six floors and a west wing of five. A three-story semicircular block projects from the north side and is decorated with three mosaic panels. (Architects: Messrs. Easton and Robertson, Cusdin, Preston, and Smith.)

Geigy Expansion

Opening new Geigy buildings for research and administration at Manchester last week, Mr. R. Maudling, President of the Board of Trade, praised the "enormous vigour" of the chemical industry and its important contribution to the export trade. Some expansion was bound to continue, he said, but competition was bound to get stronger too. The British Government welcomed the growing contacts between British and Swiss industry. The closer they worked together the better it would be for both of them.

Training for Midwifery

The General Nursing Council and the Central Midwives Board have agreed in principle to the provision of a three-month period of obstetric nurse training for student nurses during their general training which would enable a reduction of two months to be made in subsequent midwifery training.

Memorial to C. C. Barnard

On October 12, at the London School of Hygiene and Tropical Medicine, Sir Philip Manson-Bahr dedicated the Barnard Room in the library in memory of the late Mr. C. C. Barnard, librarian to the School from 1921 to 1959. An obituary was printed in the *Journal*, March 14, 1959, on p. 726.

Expired-air Method of Resuscitation

The St. John Ambulance Association has issued a leaflet on the expired-air method of artificial respiration which includes a discussion of the method and a brief outline of how it may be performed. Copies of the leaflet may be obtained from the Stores Manager, Order of St. John, St. John's Gate, Clerkenwell, London E.C.1 (price 3d. each plus postage).

Grants, Gifts, and Bequests

Oxford University has accepted a grant of $30,600 a year for four years from the U.S. Public Health Service for research in the department of biochemistry under the direction of Professor Sir HANS KREBS, F.R.S.

Birmingham University has accepted a Medical Research Council grant of £11,000 a year to finance research on humoral physiology and pathology under the direction of Professor I. E. BUSH.

People in the News

Mr. E. A. NICOLL, senior surgeon to the accident and orthopaedic services of the Mansfield General and Chesterfield Royal Hospitals and surgeon to the Harlow Wood Orthopaedic Hospital, is visiting Greece and Israel on behalf of the British Council.

Mr. A. V. S. DE REUCK, formerly assistant editor of *Nature*, has been appointed deputy director of the Ciba Foundation for the Promotion of International Co-operation in Medical and Chemical Research, London.

COMING EVENTS

Rubella Group for Deaf/Blind Children.—Conference: "Children with a Combined Visual and Auditory Handicap," January 7 and 8, Royal National Institute for the Blind, Condover Hall School, Condover, Shrewsbury, Shropshire. Requests for accommodation to Mrs. PEGGY FREEMAN, 63 Horn Lane, Woodford Green, Essex, by October 24.

British Postgraduate Medical Federation (London University).—Lectures designed for research workers and specialists in training: "The Scientific Basis of Medicine." From October 20, Tuesdays and Thursdays at 5.30 p.m. See Diary each week for details.

Institute for the Study and Treatment of Delinquency.—Autumn week-end conference: "Problems of Adoption," October 21–23, Burton Manor, Neston, Cheshire. Monthly series: "The Chronic Offender," Caxton Hall, London S.W.1. Details from the General Secretary, I.S.T.D., 8 Bourdon Street, Davies Street, London W.1 (Mayfair 3472).

Waller Memorial Lecture, St. Mary's Hospital Medical School.—Sir WILFRID LE GROS CLARK, F.R.S., "The Synthesis of Anatomy and Physiology in Neurological Studies," October 25, 5 p.m., at the hospital, Paddington, London W.2.

Midland Centre for Neurosurgery.—Dr. GUNNAR BRANTE (Eskilstuna, Sweden): "Some Aspects of the Composition of Nervous Tissue and its Alteration in Disease," October 27, 8 p.m., at the Centre, Holly Lane, Smethwick 41.

Heath Clark Lectures (London University).—Dr. CHARLES WILCOCKS, "Aspects of Medical Investigation in Africa." November 2, 3, 9, 10, at 5.30 p.m. For details see Diary.

Bradshaw Lecture, R.C.P.Lond.—Dr. W. I. CARD: "The Concept of Gastric Secretory Cell Mass," November 3. For details see advertisement p. 69.

Royal Society Leeuwenhoek Lecture.—Dr. A. M. LWOFF, For.Mem.R.S. (Institut Pasteur, Paris), "Viral Functions," November 3, 4.30 p.m., Burlington House, Piccadilly, London.

12th (Annual) Ciba Foundation Lecture.—Professor J. KONORSKI (Department of Neurophysiology, Nencki Institute of Experimental Biology, Warsaw): "Changing Concepts Concerning Physiological Mechanisms of Animal Motor Behaviour," November 4, 5 p.m., Royal Institute of British Architects, 66 Portland Place, London W.1. Chairman: Lord ADRIAN, O.M., F.R.S. Admission by ticket only, obtainable free from Assistant Secretary, Ciba Foundation, 41 Portland Place, London W.1 (Tel.: Museum 9456).

College of General Practitioners (East Anglian Faculty).—Day course for general practitioners on medicine, surgery, orthopaedics, obstetrics, and anaesthetics, November 6, 10.30 a.m., R.A.F. Hospital, Ely, Cambridgeshire. Details from the College, 41 Cadogan Gardens, Sloane Square, London S.W.3.

Royal Photographic Society.—Sir ROBERT PLATT, P.R.C.P., will open the Medical Group's exhibition of medical photography (November 7–22) at 7 p.m., on November 7.

Industrial Welfare Society. — Two-day conference: "Management of Women," November 8, 9, 10 a.m. to 5 p.m., Connaught Rooms, Great Queen Street, Kingsway, London W.C.2. Details from the Society, Robert Hyde House, 48 Bryanston Square, London W.1.

Frederick Price Lecture.—Lord COHEN OF BIRKENHEAD will lecture on "Changing Concepts of 'Diathesis' in Medicine" at the Royal College of Physicians of Edinburgh on November 9 at 5 p.m.

Edwina Mountbatten Trust.—Concert organized by Friends of Vellore, November 9, 7.30 p.m., Royal Albert Hall; soloist, Mr. YFRAH NEAMAN. Details and tickets (3s. 6d. to 15s.) from Friends of Vellore, 244 Ballards Lane, London N.12. (Tel. HIL 7657.)

Glasgow University Club, London.—Annual dinner, Trocadero Restaurant, London W.1, November 10, 7 for 7.30 p.m. Chairman: Lord HAILSHAM; guests: Lord BOYD ORR and Sir HECTOR HETHERINGTON. Graduates who are not members should write to Dr. J. F. HEGGIE, Department of Pathology, North Middlesex Hospital, London N.18.

Watson-Jones Lecture, R.C.S.Eng.—Dr. PRESTON A. WADE: "The Accident Surgery of Motorways," November 10, 5 p.m., at the College, Lincoln's Inn Fields, London W.C.2.

St. Thomas's Hospital Old Students' Dinner.—Savoy Hotel, London (entrance, Victoria Embankment), November 11, 7 p.m. for 7.30 p.m. Chairman: Dr. JOSEPH BAMFORTH.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

BRITISH HEART JOURNAL

A Family with Obstructive Cardiomyopathy (Asymmetrical Hypertrophy). A. Holman, J. F. Goodwin, D. Teare, and J. W. Renwick.
Right Ventricular Pressure Curves in Congenital and Acquired Heart Disease. R. Shanahan, G. S. Myers, E. Del Campo, A. L. Friedlich, and G. Scannell.
Ventricular Mechanics and Intracardiac Electrogram in Experimental Bundle-Branch Block. G. Folli, E. Vitolo, G. G. Battioni, and G. P. Zocche.
Pulmonary Valvotomy and Infundibulectomy. F. Ronald Edwards.
Haemodynamic Studies in High Output Beri-Beri. R. B. Blacket and A. Jean Palmer.
Cardiac Myxomata and Aortic Saddle Embolism. A. Barham Carter, K. G. Lowe, and I. G. W. Hill.
The Auscultatory Findings in Hypertension. John Barlow and Priscilla Kincaid-Smith.
The Effect of Hypothermia on Atrial Fibrillation and other Arrhythmias. Walter Somerville.
Peripheral Venous Pooling and Left Atrial Pressure Pulse in Mitral Disease. P. G. F. Nixon.
Results of Surgical Treatment for Pulmonary Atresia. Maurice Campbell.
Dye Dilution Curves in Congenital Heart Disease. C. Oakley, S. Taylor, D. Wilcken, A. Holman, J. F. Goodwin, and J. Shillingford.
The Phonocardiogram in Endomyocardial Fibrosis. K. Somers and A. W. Williams.
The Significance of Deep S Waves in Leads II and III. Hywel Davies and William Evans.
The Weight of the Ventricles in the Later Weeks of Intra-uterine Life. John L. Emery and M. S. MacDonald.
Effect of Priscol on the Pulmonary Circulation in Cor Pulmonale. J. Widimsky, J. Kasalicky, A. Valach, R. Dejdar, Z. Vyslouzil, and M. Lukel.
The Chiari Network and the Valve of the Inferior Vena Cava. Elinor D. U. Powell and Joan M. Mullaney.
Proceedings of the British Cardiac Society.
Case Reports.

Volume 22, No. 4. (Quarterly; £3 annually.)

BRITISH JOURNAL OF VENEREAL DISEASES

Editorial
Flagyl in the Treatment of Trichomoniasis. P. Rodin, A. J. King, C. S. Nicol, and J Barrow.
Flagyl (8823 R.P.) in the Treatment of Trichomoniasis. C. S. Nicol, J. Barrow, and A. Redmond.
Flagyl (Metronidazole). P. Durel, P. Couture, P. Collart, and C. Girot.
Incidence of Trichomonas vaginalis in Marital Partners. L. Watt and R. F. Jennison.
Epidemiological Aspects of Human Trichomoniasis. R. R. Willcox.
An Imidazole Derivative (Flagyl) Effective Orally in Vaginal Trichomoniasis. R. R. Willcox.
Comparison of the Fluorescent Treponemal Antibody Test with Other Tests for Syphilis on Cerebrospinal Fluids. Ad Harris, H. M. Bossak, W. E. Deacon, and W. L. Bunch, Jr
A Study of the Aetiology of Non-Gonococcal Urethritis and Reiter's Disease. G. W. Csonka and G. Furness.
Local Hydrocortisone in Peyronie's Disease. S. Ghosh, R. Ghosh, and S. Sen.
Influence of Methyl Prednisolone on the Outcome of the Treatment of Acute Gonorrhoea in the Male with Tetracycline. R. R. Willcox.
Future Problems of Venereal Disease Control Affected by Increased Teenage Population. M. B. Loeb.
Seventh Annual Symposium on Antibiotics. R. R. Willcox.
Abstracts.

Volume 36, No. 3. (Quarterly; £3 annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 24

MANCHESTER MEDICAL SOCIETY: SECTION OF ODONTOLOGY.—At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Presidential Address by Dr. J. Miller: Five Dental Hospitals of Manchester.
POSTGRADUATE MEDICAL SCHOOL.—4 p.m., Dr. J. Vallance-Owen: Insulin Activity and Antagonism in Plasma.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. H. Watson: Investigative Techniques in Cardiology II.

Tuesday, October 25

ABORTION LAW REFORM ASSOCIATION.—At Conway Hall, Red Lion Square, London W.C., 7.15 p.m., Dr. G. I. M. Swyer: Oral Contraception.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. C. H. Andrewes: Common Cold.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. Brian Russell: Bacteria on the Surface of the Skin.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Mr. H. J. Seddon: Peripheral Nerve Injuries.
MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., university lecture on the History of Medicine by Dr. D. J. Williams: Epileptic Patients a Century Ago.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Professor Ian Aird: Blood Groups and Disease.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Harben Lecture by Professor R. A. Kehoe (Cincinnati): Metabolism of Lead in Man in Health and Disease (illustrated)—(1) "Normal" Metabolism of Lead.
ST. ANDREWS UNIVERSITY.—At Anatomy Department Lecture Theatre, 5 p.m., Dr. J. D. B. Macdougall: Methods in Tissue Culture I.
ST. MARY'S HOSPITAL MEDICAL SCHOOL: WRIGHT-FLEMING THEATRE.—5 p.m., Sir Wilfrid Le Gros Clark, F.R.S.: The Synthesis of Anatomy and Physiology in Neurological Studies.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. E. H. Larkin: Drug Treatment in Psychiatry.

Wednesday, October 26

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Ringworm Fungi.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. O. S. Tubbs: Cardiac Surgery in the Older Age Group.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. W. N. Mascall: Gonococcal Urethritis.
●LEEDS UNIVERSITY.—At General Infirmary at Leeds, (1) 5 p.m., Dr. R. R. Macdonald: Cervical Mucus. Twins. (2) 6 p.m., Mr. D. W. Currie: Anatomy of the Pelvic Floor and Prolapse.
POSTGRADUATE MEDICAL SCHOOL.—2 p.m., Dr. J. H. Wilkinson: Biochemistry of the Thyroid.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., Sydney Watson Smith Lecture by Sir Stanley Davidson: Anaemia and Operations on the Gastro-intestinal Tract.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arnott Demonstration by Dr. D. H. Tompsett: Injection of the Blood Vessels of the Heart with Synthetic Resin.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF UROLOGY.—At Royal College of Surgeons, 5 p.m., Urology Lecture by Mr. D. M. Wallace: Carcinoma of the Bladder.
ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Dr. Ian Mackay (Melbourne): Lupoid Hepatitis.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Harben Lecture by Professor R. A. Kehoe (Cincinnati): Metabolism of Lead in Man in Health and Disease (illustrated)—(2) Metabolism of Lead under "Abnormal" Conditions.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Professor D. M. Douglas: Investigation of Peripheral Circulation in Limbs.

Thursday, October 27

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor Wilson Smith: Virus Flocculation Reactions.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. D. Calnan: Itching, Physiological and Pathological.
LIVERPOOL MEDICAL INSTITUTION.—Mr. E. Parry: The Organization of Medical Services in Kuwait and the Arab Countries.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Thomas Vicary Lecture by Dr. C. E. Dukes: Genetics in Relation to Surgery—A Historical Review.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Harben Lecture by Professor R. A. Kehoe (Cincinnati): Metabolism of Lead in Man in Health and Disease (illustrated)—(3) Present Hygienic Problems Relating to the Absorption of Lead.
ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. R. Schilling: Recent Studies of Chronic Respiratory Disease in Textile Workers.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Hamilton Paterson: postgraduate demonstration in neurology.

Friday, October 28

INSTITUTE OF DENTAL SURGERY, EASTMAN DENTAL HOSPITAL.—4.30 p.m., Wilkinson Lecture by Lord Cohen of Birkenhead: Diagnostic Significance of Pain.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. M. Feiwel: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—At 11 Chandos Street, London W., 6.45 for 7.30 p.m., annual general meeting; 8.45 p.m., general meeting. Dr. R. S. Morton: Intramuscular Terramycin Therapy in Non-gonococcal Urethritis.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields Hospital, 8.30 p.m., clinical evening.
POSTGRADUATE MEDICAL SCHOOL.—(1) 10 a.m., Mr. G. E. Mavor: Some Aspects of Arterial Grafting in Atherosclerosis of the Lower Limb Arteries. (2) 4 p.m., Dr. G. de J. Lee: Pulmonary Vascular Homoeostasis in Man.
ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS, 27 Sussex Place, Regent's Park, London N.W., 5 p.m., Wiliam Blair-Bell Memorial Lecture by Mr. Ian MacGillivray: Hypertension in Pregnancy and its Consequences.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. K. G. Lowe: Modern Concepts of Heart Failure.
●SOUTHEND-ON-SEA HOSPITAL.—At Recreation Hall, General Hospital, Rochford, 8.30 p.m., Sydney Body Lecture by Dr. Harley Williams: Medicine and the Unknown.

Saturday, October 29

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Chest Clinic, Castle Hill, Cambridge, Symposium on Respiratory Diseases. Morning: 10.30 a.m., Mr. B. B. Milstein: Thoracic Surgeon and the General Practitioner; 11.30 a.m., Dr. M. J. Greenberg: Spontaneous Pneumothorax; 12.15 p.m., Dr. L. C. Lum: Cor Pulmonale. Afternoon: 2.15 p.m., Mr. C. Parish: Place of Surgery in Pulmonary Tuberculosis; 3 p.m., Dr. R. A. Bruce: Eosinophil and Respiratory Disease; 3.45 p.m., Dr. K. H. Nickol: Bronchiectasis.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 11.15 a.m., Professor I. Donald: Modern Diagnostic Aids in Obstetrics.

Sunday, October 30

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., Seminar by Mr. S. E. Birdsall: Common Ear, Nose, and Throat Conditions.
MANCHESTER UNIVERSITY: FACULTY OF MEDICINE.—At Theatre I, Clinical Sciences Building, York Place, Manchester, 11 a.m., in conjunction with North-west England Faculty, College of General Practitioners. Professor J. H. Kellgren, Dr. B. Portnoy, and Dr. P. S. Byrne: Place of the Corticosteroids in General Practice.

APPOINTMENTS

CAPON MARGARET V., M.B., B.S., Assistant County Medical Officer and School Medical Officer, Northamptonshire County Council.
HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London W.C.—W. J. Glover, M.B., B.Ch., F.F.A. R.C.S., D.Obst.R.C.O.G., Consultant Anaesthetist; J. A. Dudgeon, M.D., Consultant Pathologist in charge of Department of Microbiology; J. D. Atwell, M.B., Ch.B., F.R.C.S., Surgical Registrar.
LONDON COUNTY COUNCIL.—A. T. Evans, M.R.C.S., L.R.C.P., D.P.H., and R. G. Isaac, M.R.C.S., L.R.C.P., Whole-time Medical Officers in Public Health Department.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Valentine.—On October 8, 1960, at the Women's Hospital, Nottingham, to Catherine Mary (formerly Birtles) and Dr. Anthony S. Valentine, a daughter—Alison Mary.
Watts.—On October 3, 1960, at the Central Middlesex Hospital, London N.W., to Shelagh (formerly Wimhurst), M.B., B.S., F.F.A.R.C.S., and K. Dawson Watts, F.D.S.R.C.S., a brother for Susan—Richard Kelsey.

DEATHS

Gibbons.—On September 27, 1960, at 33 Bridgefield, Farnham, Surrey, Arthur Philip Gibbons, M.B., aged 88.
Lewis.—On September 26, 1960, at Guy's Hospital, London S.E., Charles Bernard Lewis, M.B., Ch.B., of Caterham, Surrey, aged 60.
McCann.—On September 27, 1960, at Brackness, Berks, Michael McCann, M.B., B.Ch., of 2 Burcote Road, Wandsworth Common, London S.W., formerly of 64 Trinity Road, London S.W., aged 93.
Shepherd.—On September 23, 1960, in a nursing-home, Winchester, Hants, Charles Ernest Alan Shepherd, M.R.C.S., L.R.C.P., D.P.M., late of Chartham, Kent.
Wells.—On September 8, 1960, at Whitehall Court, Rondebosch, Capetown, South Africa, Alexander Simpson Wells, M.D., F.R.C.S.Ed.
White.—On September 24, 1960, in a nursing-home, Robert Oliver White, L.R.C.P.&S.I. and L.M., of Four Marks, Hants, formerly of Ealing, London W., and Gold Coast, West Africa, aged 82.

Any Questions

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Potency of Thyroid Extract

Q.—*Are some batches of thyroid extract less effective than others? Does efficacy of thyroid extract fall off with time? If so, what time limits are acceptable for keeping thyroid extract in a dispensary? Should thyroxine be used routinely instead of thyroid extract?*

A.—In this country the term "thyroid extract" is an official synonym for thyroid *B.P.* This preparation is not standardized by its biological activity but by chemical assay of its iodine content. This is because the chemical method is simpler and more accurate than biological standardization and because it has always been believed that there was a close correlation between iodine content as measured by the official method of assay and biological activity. Recently some doubt has been cast on the validity of this assumption, and it is now thought that different preparations of thyroid, even if they conform to the official standard, may vary in potency. In addition, there are available preparations which contain more or less iodine than the *B.P.* standard, and their clinical efficacy will therefore vary. When thyroid is used it should always be prescribed as thyroid, *B.P.*, or tab. thyroid., *N.F.*, and not in terms of fresh gland.

Both the *British Pharmacopoeia* and the *National Formulary* recommend that thyroid tablets should be stored in a cool place and in containers which prevent access of moisture. If this is done their efficacy probably does not fall off with time. Although it has been suggested that thyroid tablets lose their potency when they are more than three months' old,[1] both chemical assay and tests of biological activity have shown that such tablets may still retain their potency even after 17 years.[2 3]

Thyroxine is a synthetic hormone of constant chemical composition. The difference in cost between maintenance therapy with thyroxine and the equivalent amount of thyroid is now negligible.[4] For these reasons thyroxine, as thyroxine sodium tablets, *B.P.*, or tab. thyroxin. sod., *N.F.*, should be regarded as the drug of choice for the treatment of hypothyroidism.

References

1 Jackson, A. S., *J. Amer. med. Ass.*, 1957, **165**, 121.
2 Wermer, P. L., ibid., 1958, **166**, 401.
3 Hubata, J. A., McCall, P. J., and Douglass, T., ibid., 1958, **166**, 402.
4 Wayne, E. J., *Brit. med. J.*, 1960, **1**, 83.

Local Reaction to Pertussis Vaccine

Q.—*If a baby experiences a severe local reaction to 1 ml. of suspended pertussis vaccine, with much swelling and redness of the arm and shoulder, subsiding in about 24–48 hours but leaving a small nodule, is it wise to proceed with the course of injections? Can the injections be proceeded with but further reactions avoided?*

A.—In the Medical Research Council's whooping-cough vaccine trials about 60% of the 940 children visited 24–48 hours after each injection showed some kind of reaction; all but nine had mild malaise of 24–48 hours as well as a local reaction[1] (a severe local reaction without some degree of general reaction is unusual). Reactions were not confined to any one of the three injections; some occurred after the first, some after the second, and some after the third. Three of the nine children with severe reactions were given subsequent injections without ill effect. Thus it appears that unpredictable reactions do occur frequently and haphazardly.

It is impossible to give a straight or dogmatic answer to the question: every such case must be considered on its own merits. The decision whether to continue the course of injections must be taken by the doctor, after considering (1) the baby's age; (2) its environment and the need for full protection against whooping-cough; and (3) the attitude of the parents. If the child is nearly a year old, the most dangerous period for whooping-cough is nearly over. It may be considered unnecessary to continue the course of immunization if there is no infection in the family or likely contacts of the baby. If, however, the parents are particularly anxious that the baby should be completely protected, the other injections might be given. Another painful reaction might occur, but (and this is just as likely) it might not.

The mention of a persisting nodule suggests that the first injection may have been very superficial; it might be better if the later injections were deep subcutaneous or intramuscular. An additional precautionary measure would be to give a detector, or trial, dose of 0.1 ml. before administering the full dose.

Reference

1 *Brit. med. J.*, 1956, **2**, 454.

Where to Winter

Q.—*A man aged 55 wants to know the best place to retire to. He suffers from long-standing bronchiectasis and nasal sinusitis with symptoms which seem to vary with the weather.*

A.—One may go further than the patient, and assert that his symptoms undoubtedly do vary with changes in the weather. It is clear, therefore, that he needs for retirement a resort in which their aggravation is minimal. The essential qualities of a suitable climate are equable temperature, plenty of sunshine without heat, moderate humidity, and, of course, pure air.

If circumstances and opportunities are unlimited and unqualified—a most improbable stipulation—one would advise wintering in Assuan in upper Egypt, 590 miles south of Cairo, so long as possible, only migrating when heat demands. In my experience no more desirable climate can be selected, and desert air is particularly agreeable. Madeira has advantages that its mean annual temperature is about 65° F. (18.3° C.) and that the average daily variation does not exceed 10° F. (5.5° C.). Madeira is, of course, more accessible, and for other reasons is on the whole more suitable for a protracted stay. But if (as one suspects) the patient is considering the British Isles, one can only regret the impossibility of dogmatism, in view of the notorious variability and frequent abrupt changes of our climate. He would do best in the winter in Cornwall generally; in the summer, the New Forest. Yet if compelled to compromise, in order to remain static throughout the year, Ventnor, Hastings, Bournemouth, or Penzance may be recommended, the choice depending upon individual tastes in recreation and hobbies.

Dietary Protein and Cystinuria

Q.—*A young woman is suffering from cystinuria and has been advised to avoid meat, fish, and eggs. She is now 3½ months pregnant. Should this diet now be relaxed?*

A.—Protein restriction in the diet in the treatment of cystinuria has certainly been recommended in the past. Recent studies, however, show that this is of no practical benefit, since, in order to reduce the cystine excretion in the urine by this means, the protein restriction has to be so severe as to be inadequate for general nutrition. Likewise a very high protein intake does not appreciably increase the cystine excretion, hence protein restrictions of any kind are no longer advised.

The best current treatment is to maintain a high rate of urine excretion throughout the 24 hours, with especial reference to the night period when concentrated urine potentially capable of forming cystine stones is almost always formed. This patient should be advised to drink, say, three pints (1.7 litres) of fluid spread out during the day, but especially she should also drink two glasses of any fluid before going to bed, and another two glasses in the early

morning. Her full bladder should normally wake her during this time; if not she should buy an alarm clock. This treatment is, of course, to be continued throughout the patient's life, since the condition of high cystine excretion is permanent. It is not too difficult to achieve such a routine if its importance to the patient is stressed sufficiently. It is a good thing to collect urine and measure the volume in four-hour periods over two days every year or so as a check on the patient's treatment. The volume should be over 500 ml./4 hr. period, but it does not matter if one of them is a little less. The giving of alkalis (say, a few g./day of sodium bicarbonate) may be helpful but is no substitute for the water-drinking routine.

There is no special advice to be given during pregnancy. Most cystinuric patients go through this without the least complication. The only known problem concerns those cystinurics who already have multiple small stones in their renal pelves. With the changes occurring in the urinary tract during pregnancy, these stones are much more likely to become detached and travel down the ureters, eventually to be passed. One should therefore look carefully for symptoms of renal colic. If the stones are passed satisfactorily this is, of course, good for the patient.

Since cystinuria is a hereditary disease inherited from a recessive gene, the patient's children will not have cystinuria.

Polaroid Glasses

Q.—*Is it possible to get untinted polaroid glasses?*

A.—Polaroid glasses are of necessity tinted.

Vaccines for Rheumatism

Q.—*Have "rheumatic" vaccines, containing mixed streptococci, any place in the treatment of rheumatism?*

A.—The word "rheumatism" is too wide to convey the idea of any exact diagnosis: any ache or pain may receive this title. In none of the many types of arthritis are vaccines of any help, though the production of a fever or systemic reaction by any means does sometimes produce an improvement for a time: intravenous pyrogen therapy has, however, largely been given up. In terms of the common types of arthritis, rheumatoid and osteo, the quick answer to this question is, in the opinion of most workers in the field of rheumatology to-day: No.

Inheritance of Ichthyosis

Q.—*A baby aged three months has recently died with a very severe ichthyosis and secondary infection. The mother is anxious to know if, in the event of her having another child, it would be born with the same complaint. There is no family history of ichthyosis.*

A.—Ichthyosis is a congenital abnormality of keratinization usually affecting more than one member of a family. It is transmitted by a single gene as a recessive characteristic. Sometimes relatives may show only very mild ichthyosis, occasionally only hyperkeratosis of the palms or soles, and this suggests that in heterozygous carriers of this gene the trait may not always be entirely recessive to the normal. It is very unlikely indeed that this mother may give birth to another severely ichthyotic child.

Raynaud's Disease and Impotence

Q.—*A man aged 52 has been completely impotent for one year and has had Raynaud's disease for five years. Would the latter have any bearing on the impotence?*

A.—Though the existence of Raynaud's disease naturally suggests the possibility of a vascular cause for this patient's impotence, it is unlikely that the relationship is much more than fortuitous. This would seem especially to be so since the Raynaud's disease antedated the impotence by four years. There are many impotent men of 52 without physical or obvious psychological cause, and in most of these the age factor, together with less obvious psychological causes, are to be held responsible.

NOTES AND COMMENTS

Health Precautions in the East.—Lieutenant-Colonel H. H. King (Chalfont St. Giles, Bucks) writes: In case your correspondent ("Any Questions?" September 3, p. 748) who is taking a post in "the Madras region of India" may think he is doomed to give his family antimalarial drugs during the whole of his stay, may I remind him and the giver of your advice that he may not have to use such drugs? It is entirely a matter of whether malaria-carrying anophelines are or are not found in the locality in which he will be living. This he can learn from his local doctor. In many parts of the Madras region of India—a very vast and varied region—such anophelines are not found. In any case he would do well not only to take preventives but also to use mosquito nets when travelling.

Dr. F. S. Hawkins (High Wycombe, Bucks) writes: In the *Journal* of September 3 ("Any Questions?" p. 748) a question is asked about the risks to a family, particularly to the baby, going to Madras. May I suggest that B.C.G. vaccination before going would be most important?

Our Expert replies: When giving advice to those going overseas it is important to be sure that that advice will deal fully with the problem and leave a margin of safety. It must, moreover, be capable of being immediately applied, for illness and, in some regions, deaths are still occurring as a result of delay in applying malaria precautions. Advice of the kind "He can learn from his local doctor" is usually worthless. In the rush of things to do on arriving in a new country a person may well be unable to seek out a local doctor for some time and by then be already ill from malaria. Antimalarials are now so free from toxic effects that it is much better to take a prophylactic unnecessarily than to run the risk of what can be a fatal illness. Colonel King's final sentence appears, in any case, to invalidate his earlier comments.

Dr. Hawkins's comment arouses many issues on which opinion is as yet divided. The ability of B.C.G. vaccination to produce increased resistance to infection with virulent bacilli and to development of progressive disease awaits full statistical proof, and its use would appear to present a general rather than a specifically tropical problem. The consensus of opinion in this country appears to be to advise its use only for specially exposed groups, and it is very doubtful whether those going to India should be so classified.

Up on the Points.—Dr. G. Mitchell (Inverness) writes: With reference to your answer ("Any Questions?" September 24, p. 958) to the question of the advisability of going "on her points" at the age of 10—may I point out that no reputable ballet teacher or ballet school permits a child to do so until after her figure has formed, because of the change in poise and balance which this entails. The age of 13 or 14 should be the earliest at which points should be permitted. Reference to any ballet school will confirm this information.

Our Expert replies: While it may well be the practice of ballet schools not to allow a child to go up on her points before the age of 13 or 14, I cannot see why this should have any significant effect upon poise and balance before this age.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

All communications with regard to editorial business should be addressed to THE EDITOR, British Medical Journal, B.M.A. House, Tavistock Square, London W.C.1. Telephone: EUSTON 4499. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: EUSTON 4499. Telegrams: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. Telephone: EUSTON 4499. Telegrams: *Medisecra, Westcent, London.*

B.M.A. Scottish Office: 7 Drumsheugh Gardens, Edinburgh.